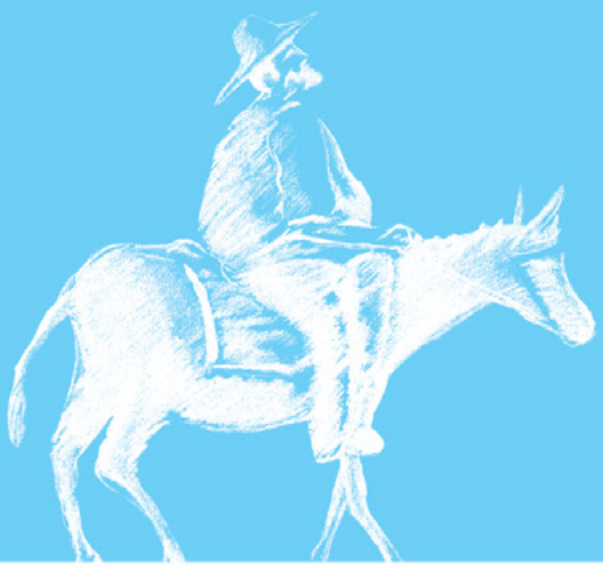
INCT OF DRUGS AND MEDICINES



2010

ANNUAL ACTIVITIES REPORT

2010

ANNUAL ACTIVITIES REPORT

INCT OF DRUGS AND MEDICINES

The allegory created by Miguel de Cervantes in Don Quixote expresses the human search for knowledge and truth. The image on the cover shows the pilgrimage of the character of Sancho Panza, Don Quixote's squire, gazing upon a constellation of chemical structures, which are the object of study at INCT-INOFAR, not passively, but trying to uncover the truths it contains.

DR. ANGELO DA CUNHA PINTO

CNPq Process number 573.564/2008-6
FAPERJ Process number E-26/170.020/2008

inct inofar
instituto nacional de ciência e tecnologia de Fármacos e Medicamentos
www.inct-inofar.ccs.ufrj.br

SUPORT

CNPq 60 ANOS
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FAPERJ Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro
inct institutos nacionais de ciência e tecnologia

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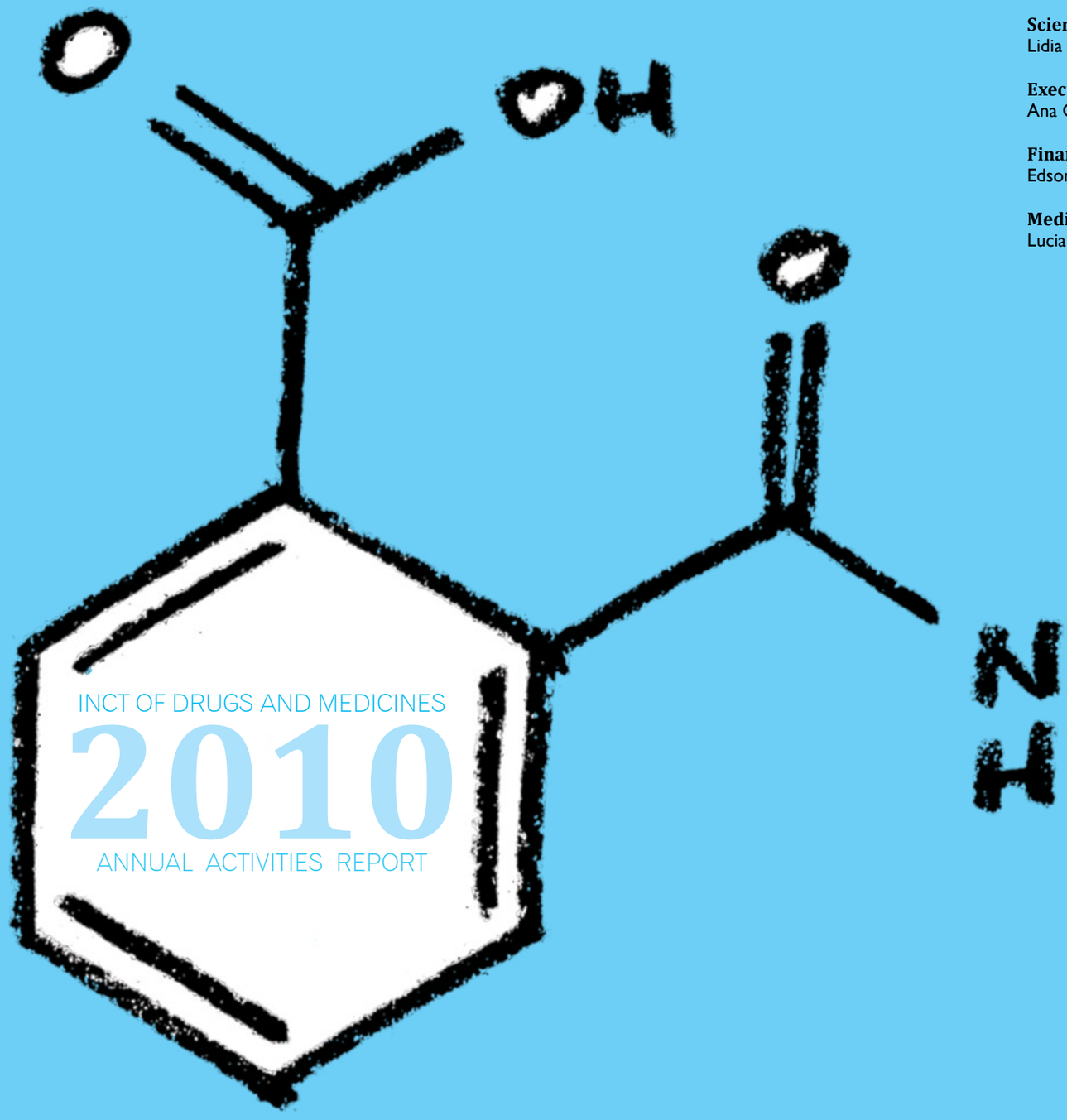
INCT OF DRUGS
AND MEDICINES

**Development of science,
range of health**



INCT OF DRUGS AND MEDICINES

2010

ANNUAL ACTIVITIES REPORT

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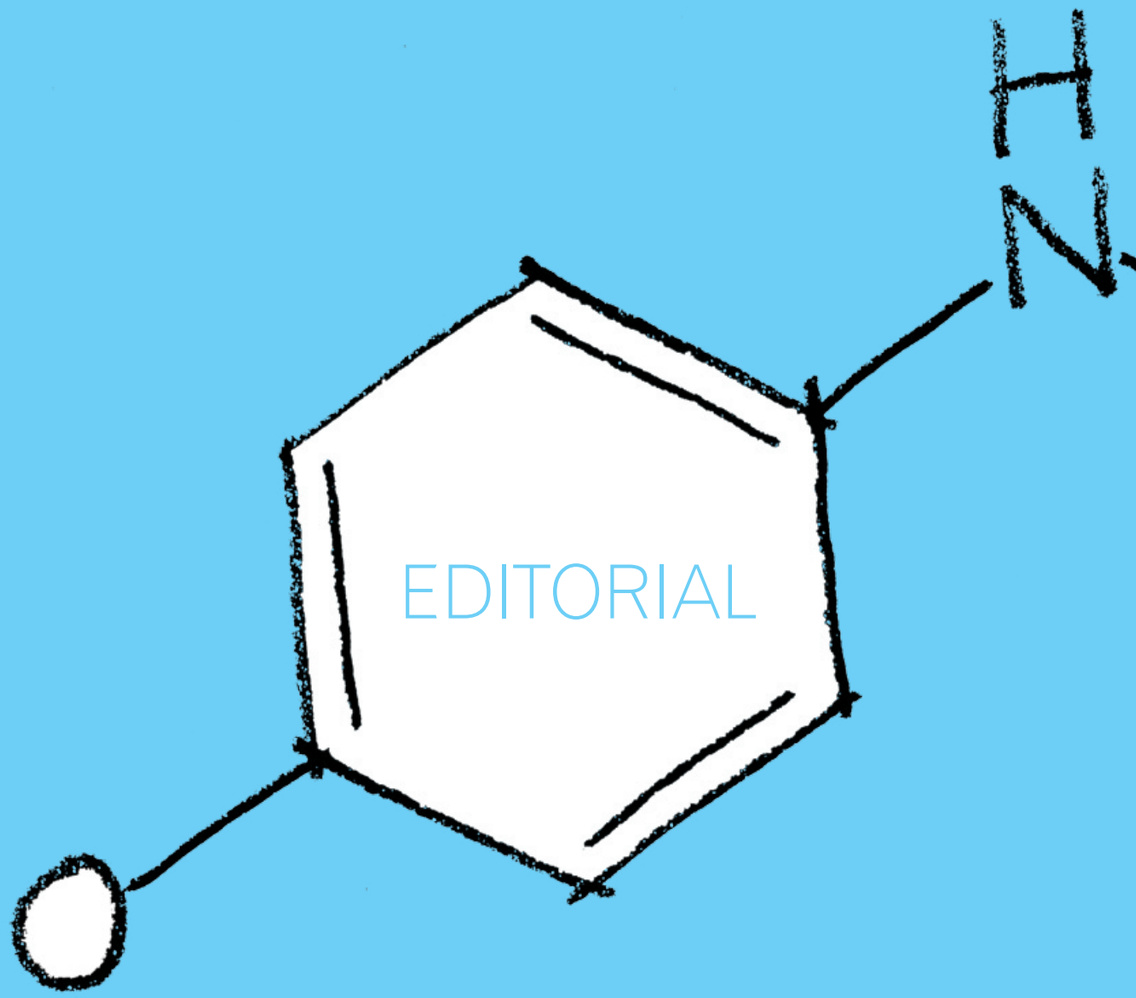
2010

ANNUAL ACTIVITIES REPORT

INCT OF DRUGS AND MEDICINES



EDITORIAL

INCT-INOFAR
Annual Activities Report
2010

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Editorial

The civilized nations could not depend only of imported pharmaceuticals from foreign nations to promote the health of their population. We are still at the beginning stages of inventing or discovering new pharmaceuticals, and we depend on the capacity for invention/innovation or discovery of other countries to incorporate these therapeutic novelties to our therapies. As such, we pay high prices for this serious technological dependence. In spite of this worrying picture, we have had a few important advances. We have moved forward in the area of generic medications, widening a bit, although less than what is necessary, the pharmaceutical care to the portion of our population that requires use of these medications. Recently, the People's Pharmacy program was created by the federal government, which made for a more human care for low income patients with chronic illnesses of high morbidity, taking care of those in financial need and elderly people, especially retired people. However, even in these areas that show a relative advance, there are still important standstills due to more political resolutions. We have extreme dependence on foreign countries, because very little of what we need in terms of pharmaceuticals are things that we have the know-how or the technology to do. We still import the vast majority of pharmaceuticals – active principles – that will become the generic pharmaceuticals we will use, even in the government health care programs, from far away suppliers often located in China, India, or Korea. This is a situation of extreme external dependence, which compromises national sovereignty. In our country, we aim to build in a few decades, but with hard work from several different social actors, all motivated and imbued with the purpose to be qualified in graduate education and scientific research, creating a modern, efficient, and enviable system of graduate education, able to award *ca.* 12,000 PhD titles a year, in practically every area of scientific, technological, humanities, and art knowledge. Although it is still undersized when compared to our real needs and to our population of *ca.* 192 million Brazilians, according to the 2010 Census data, this admirable contingent of qualified people is living the so-called "Era of Knowledge", of continuous technological advancement, in almost exclusively academic environments, due to the small numbers of PhDs working in the private sector. We have the reassurance of having a positive effect in that area, improving the qualification of our graduate students as they have qualified professors in their courses, but we do not qualify people for the work positions in the Brazilian industry, including the pharmaceutical industry. There are some attempts, here or there, sometimes, in a true make believe, but there is no qualified corporate space similar to the one observed in the developed world, or even in the developing world, yet. This also makes the effective and real proximity of corporate world and university, making the transfer of Brazilian technologies not viable under these adverse conditions.

www.inct-inofar.ccs.ufrj.br

Conscious of this reality, we at the National Institute for Science and Technology in Drugs and Medicines (INCT-INOFAR) have defined at our Governance and Follow-Up Committee (CGA/INCT-INOFAR) the main goals for 2010, with the intensification of our research activities, through subprojects, both those classified as radical innovation and those classified as incremental innovation. In this case, priorities have been defined, identifying the two substances being studied since the previous year. It was also decided that we should promote constant evaluation of the goals of each subproject under study, through quarterly reports and through workshops. For this goal, the support of the Scientific Superintendence of INCT-INOFAR was decisive. It was defined also, among priority actions for 2010, to vividly encourage mobility of participating graduate students and researchers, to strengthen the scientific exchange between experts from different

laboratories, as a way to contribute to the advancement and the meeting of the deadlines in the goals and objectives schedule. Throughout the year, we had the satisfaction of seeing evident progress, whether through its various accomplishments as co-organizing scientific meetings or scientific awareness activities, or through the advances achieved in subprojects of our portfolio, showing excellent levels of scientific maturity, we have reviewed the classification of one of the priority projects due to unexpected toxicity results. We have reached, in this period, important results in the study of the synthetic route for the most sold pharmaceutical worldwide, atorvastatin, with a recently expired patent, making it a generic medication in major pharmaceutical markets including Brazil. This result by itself shows the scientific capacity present in INCT-INOFAR, able to respond to important challenges, like this one that we imposed on ourselves, attesting unequivocally that we are qualified in incremental innovation. New pharmaceuticals that will be future generics are being studied. In the realm of radical innovation, the new molecules being studied have advanced in the chain of innovation, however we did not achieve success in the serious bottleneck caused by scaling, having successfully achieved pre-clinical trial stage with an important anti-asthmatic pharmaceutical candidate, innovative in its action mechanism, without being able to complete, however, the chronic toxicity studies under certified conditions, as we do not have a scale-up laboratory. Efforts are being made so we can overcome this limitation.

In what concerns the promotion of scientific awareness and the popularization of the sciences of Pharmaceuticals and Medications, we have conducted a lot of activity, always promoting the safe and rational use and contributing to fighting harmful practices like self-medication and the recommendations of pharmaceuticals by drugstore attendants. We act publicizing vaccination campaigns and we have created and edited the "Booklet on the correct use of antibiotics", which was recently made available at the National Health Surveillance Agency website (ANVISA). Several interactive actions with other INCTs have been carried out, including in the 15+ group.

portal.anvisa.gov.br/cartilha.pdf
www.inct-inofar.ccs.ufrj.br/i5.html

We consider INCT-INOFAR to have been able to positively respond to the challenges it has imposed on itself, carrying out intense scientific activity in the studies conducted in its different subprojects, with several publications in qualified periodicals with a good level of impact, supporting graduate courses in the areas of Chemistry, Pharmacy, and Pharmacology and contributing to the qualification of graduate students.

As we reach our conclusion, we highlight that this editorial is followed by the evaluation opinion of the other members of the CGA on the performance of INCT-INOFAR. We also thank our financing agencies and all our colleagues, as well as the support people from the Scientific, Executive, Finance, and Communication Superintendence as well as the other members of INCT-INOFAR.

Rio de Janeiro & Ribeirao Preto, May 31, 2011.

Eliezer J. Barreiro
Coordenador do INCT-INOFAR

Fernando de Queiróz Cunha
Vice-Coordenador do INCT-INOFAR

ANGELO DA CUNHA PINTO

When placing the synthesis of generic pharmaceuticals with patents about to expire or that have already expired as one of its top priorities, as well as the genesis and development of NEW PHARMACEUTICALS, the researchers of the INCT of Drugs and Medicines have changed the paradigm of pharmaceutical research in Brazil when they successfully synthesized ATOVASTATIN on a bench scale.

As they accepted the challenge to begin with the synthesis of atorvastatin, the leader medicine in the world market, with sales of 13 billion US dollars in 2009, the researchers of the Chemistry Institute of INCT have shown plenty of boldness and competence.

The synthesis of atorvastatin, a molecule with high structural complexity and with two stereogenic centers, by the group at the Institute of Chemistry at UNICAMP, led by Professor Luiz Carlos Dias, shows that it is possible to achieve RADICAL INNOVATION in Brazil, and that the Brazilian generic pharmaceutical market does not depend on China and India. Why then do Brazilian generic pharmaceutical companies import the active principles from these two countries, if our own country has research groups highly qualified in organic synthesis? The answer is simple: in spite of Brazil having excellent organic chemists with expertise in synthesis for the development even of new synthesis routes for any generic medication, we still lack a connection between the bench scale in university laboratories and the reactors of the production laboratories of pharmaceutical industries. This is the great bottleneck that makes Brazil a lead generic pharmaceutical importer.

The knowledge of the synthesis of generic pharmaceuticals is a great step to reach the creation of new pharmaceuticals, which is one of the goals of the INCT of Drugs and Medicines. We are overdue for BNDES to exercise its role as a propeller in making Brazil a player in the discovery of new pharmaceuticals and in the production of generic medications, as it has been doing with other sectors of industry in Brazil. It is time that BNDES finance scale-up laboratories to be shared between pharmaceutical companies, government research and development agencies, and universities.

Only with a State policy for the pharmaceutical sector will Brazil achieve the yellow-and-green pharmaceutical, and for this to happen, we cannot have funding for the INCT of Drugs and Medicines be discontinued.

The first step has already been taken by the INCT of Drugs and Medicines with the synthesis of atorvastatin. This is the first in several generic pharmaceuticals that may be synthesized by INCT researchers, who tenaciously carry on working on the discovery of new pharmaceuticals.

Angelo da Cunha Pinto
Professor of Chemistry
Federal University of Rio de Janeiro, BR
*CGA/**INCT-INOFAR***

HELOISA DE OLIVEIRA BERALDO - UFMG

The Brazilian National Institute of Science and Technology of Drugs and Medicines, or *Instituto Nacional de Ciência e Tecnologia em Fármacos e Medicamentos* (INCT-INOFAR) connects a network of researchers with expertise in different areas with the common goal of contributing to innovation and drug discovery. Our team deals either with the design of new pharmaceuticals or the development of innovative synthetic routes for generic pharmaceuticals. We have succeeded in developing novel anti-asthmatic, anti-schizophrenia and analgesic compounds that are now in advanced pre-clinical trials. A novel and less expensive route for the synthesis of atorvastatin, which will have a positive impact in the Brazilian Health Care system, has been developed by members of our team. Additionally, INCT-INOFAR supports research in new pharmaceuticals for the treatment of neglected diseases. INCT-INOFAR is also committed to the popularization of science and to direct interaction with the public from communities and *favelas* (slums) in order to provide health education. INCT-INOFAR has created the Pharmaceuticals Portal as a channel for scientific information and education, and to supports scientific journalism projects. Therefore, INCT-INOFAR has succeeded in its ambitious goals of improving scientific knowledge in drug discovery, innovation and health education in Brazil.

Heloisa O. Beraldo
Professor of Chemistry
Federal University of Minas Gerais, BR

LUIZ CARLOS DIAS – UNICAMP

INCT-INOFAR has achieved very significant results, with great potential to attract the interest of the national pharmaceutical industry. The recent discovery of novel total synthesis of atorvastatin, the active principle of Lipitor®, the best-selling drug in the world, used to reduce cholesterol levels, opens up great business opportunities for the Brazilian pharmaceutical industry. Not only for atorvastatin itself, a molecule with a high degree of structural complexity, but because it makes the academic skill level present in the country evident, which can and should be further exploited in the area of generic drugs, to obtain the active ingredients of drugs that are highly used in the National Public Health System - SUS and in the People's Pharmacy Program (Programa Farmácia Popular). The route developed for this active principle involves incremental innovations and radical innovations.

Another concern of **INCT-INOFAR** is the development of new drugs. Some promising results have been obtained in projects to control chronic lung diseases such as asthma. Encouraging results have also been achieved with regard to the demand of molecules with potential for treating neglected diseases like malaria, leishmaniasis and Chagas. Some extremely important actions of this INCT relate to the dissemination and popularization of science, such as the Virtual Institute of Pharmaceuticals, the Portal of the drugs, puzzles and booklets with cartoons, short courses and workshops are important media to alert the public about the rational use of drugs, bringing society and **INCT-INOFAR** closer.

One point that Brazil needs to move forward not only in the synthesis of active ingredients of generic medicines, but also so that we can envision the development of new drugs is an urgent need for laboratory synthesis of compounds on a larger scale. The country urgently needs to create conditions so that we can prepare on the scale of grams or kilograms, materials, active ingredients of drugs and other synthetic products and intermediates. I see this deficiency as a major impediment to the growth and strengthening the area in Brazil.

Luiz Carlos Dias
Full Professor at UNICAMP, BR

MARCO AURELIO MARTINS - FIOCRUZ

The INCT of drugs and medicines (**INCT-INOFAR**) is a multi-institutional research network marked by a broad platform of actions and projects, ranging from scientific qualification to incremental and radical innovation in drug development and pharmaceuticals. This is really a big challenge, but the results obtained so far seems to indicate that it will not disappoint. The most prominent achievement in the period was, for sure, the discovery by Luiz Carlos Dias's team (UNICAMP) of a novel route of synthesis for atorvastatin, the most widely used statin in the world, and whose patent expired in 2010. The INCT's strategy of pursuing such an outstanding synthesis proved to be correct, not only because it emphasized the competence of investigators of this INCT in a very sensitive field, but also because it effectively raised the possibility of immediate transfer of a timely technology to the pharmaceutical and pharmacochemical sector, particularly concerning generic medications. It is also positive that all the subprojects of the INCT's portfolio have been closely monitored by means of objective reports and whole-day workshops in order to prioritize those that are more advanced in the chain of innovation. Some of them are really playing well in pre-clinical settings, and the best examples are LASSBio-596 and LASSBio-579, which have been shown to be effective and safe agents for the treatment of asthma and schizophrenia, respectively. Promising findings were also obtained in other lines of investigation, concerning candidates for treatment of silicosis, a killing pneumoconiosis without satisfactory therapy so far, and trypanosomiasis, a neglected disease. Therefore, I think that **INCT-INOFAR** is doing well and indeed deserves support.

Marco Aurelio Martins
Senior Scientist
FIOCRUZ (RJ), BR

VANDERLAN DA SILVA BOLZANI - UNESP / ARARAQUARA

A brief overview of INOFAR, success, and creativity in the discovery of new pharmaceutical candidates. During the latest decade, Brazil has improved its scientific and technological capabilities and created a sustainable strategy to promote drug discovery research activities. The positive economic growth associated with a stable political structure has contributed for expanding and increasing governmental, private, and foreign investments, which are responsible for the creation of a new scenario in drug R&D in the Brazil. Furthermore, aside from this set of political and economical favorable aspects, we also have another key component in drug discovery and pharmaceutical innovation - the highest level of excellence of Brazilian researchers who work in medicinal chemistry, pharmacology and toxicology. As part of this new landscape, the Brazilian National Institute of Science and Technology of Drugs and Medicines (*Instituto Nacional de Ciência e Tecnologia de Farmácos e Medicamentos* - INCT-INOFAR) is considered a new model of the multidisciplinary research aiming to identify new pharmaceutical candidates for the improvement of human health.

In spite of the development previously achieved in this area in Brazil, the process on drug discovery remains a challenging and complex undertaking. INOFAR, under the leadership of Professor Eliezer J. Barreiro, is having extraordinarily successful performance, as for example the recent new synthetic route for obtaining the world best-selling drug atorvastatin, in semi scale-up accomplished by Prof. Luiz Carlos Dias (UNICAMP), who is another important INOFAR researcher. Aside from the synthesis of atorvastatin, the pre-clinical trials of novel anti-asthmatic, anti-schizophrenia and analgesic compounds have been developed by other members of the INOFAR team, which has also invested in the discovery of new drugs for the treatment of neglected diseases. Furthermore, the work towards the dissemination and public education on health is being carried out successfully; I consider this to be an extremely important aspect of the INOFAR strategies as it is a government-supported program. As part of this area of work, I would like to highlight the booklet about the proper use and risks of antibiotics, written by professors Lidia M. Lima and Angelo da C. Pinto (UFRJ).

As natural products researcher, I hope to find new biologically active compounds isolated from our huge biodiversity, useful for further studies in medicinal chemistry and for development, with the goal of discovering a lead molecule derived from a Brazilian plant species. That would be the realization of my greatest objective for INOFAR.

Vanderlan da Silva Bolzani
Professor of Chemistry
UNESP, BR

NATIONAL INSTITUTES
OF SCIENCE AND
TECHNOLOGY

INNOVATION IN DRUGS AND MEDICINES

INCT-INOFAR
Annual Activities Report
2010

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National Institutes of Science and Technology

www.cnpq.br/programas/inct/_apresentacao/index.html

The Program of National Institutes of Science and Technology (INCT) was created by Edict 014/2008 (MCT/CNPQ) with the purpose of promoting the creation of research networks in strategically selected areas to contribute towards sustainable development in Brazil. Articulating several associated groups or sets of research laboratories, submitted to the coordination of a host institution, the National Institutes are made up of 123 projects approved in the program, currently the largest one in the field of support to Science and Technology in the country.

The INCTs are an initiative of the Ministry of Science and Technology (MCT), established by the National Council for Scientific and Technological Development (CNPq), with partnerships with the states Foundation for Research Support (FAPERJ, FAPESP, FAPEAM, FAPESC, FAPESPA and FAPEMIG), of the Department of Science and Technology in the Ministry of Health (Decit/MS) and of the Coordination for Improvement of Higher Level Personnel (CAPES), as well as the support of the National Bank for Social and Economic Development (BNDES).

Innovation in Drugs and Medicines

INCT-INOFAR is one of 122 National Institutes of Science and Technology (INCTs) created by the Brazilian government, in 2008, to integrate research networks in subjects considered to be strategic, such as Drugs & Medicines (D & M). **INCT-INOFAR** has a mission of developing new projects in D & M research, dealing with radical innovation (*i.e.* new molecules) as well as with incremental innovation (*i.e.* generic pharmaceuticals), as well as taking part in and coordinating efforts to popularize and increase awareness about sciences related to D & M research. For this purpose, **INCT-INOFAR** is responsible for the Pharmaceuticals Portal (www.portaldosfarmacos.ccs.ufrj.br), a project inherited from FAPERJ, which functions as the web presence for the Institute.

Made up of a network of expertises articulated by 31 research groups in 14 institutions in 8 states, **INCT-INOFAR** has a goal of coordinating the carrying out of several different research subprojects, all of which relate to the complex chain of innovation in D & M. INCT-INOFAR the research necessary for carrying out all the fundamental stages in the process of discovering new drugs – from the election of the therapeutic target to the conclusion of pre-clinical trials – achieving in this manner a successful completion of all the stages of the complex chain of innovation in drugs and medicines. **INCT-INOFAR** aims to qualify technical-scientific competences in all the diverse stages of the process of discovery/invention of new drugs – from the election of the most adequate therapeutical target in the treatment of a specific physiopathology, to the conclusion of bioassays in the pre-clinical Trial stage. Another goal is to build active links between scientists and researchers involved in these subprojects with the business sector, whether government-owned or privately operated, that can absorb the technology developed. This is a priority goal in the **INCT-INOFAR** agenda.

MISSION

- To organize national scientific competences into an effective network to research pharmaceuticals and medications;
- To support multi-institutional scientific research subprojects in the discovery of new pharmaceuticals;
- To contribute to incremental and radical innovation in new pharmaceuticals and generic medications;
- To study and develop the total synthesis of generic medications, advanced intermediates and raw materials;
- To contribute to the improvement and qualification of personnel in the fields of Medicinal Chemistry and Pharmacology;
- To promote awareness of sciences related to pharmaceuticals and medications, as well as their safe and rational use.

UFC
UFPB
UFAL

UFG
USP
UNESP
UNICAMP
Cristália
Instituto Royal

UNIFAL
In Vitro Cells
UFMG

FIOCRUZ
UFRJ
UERJ
LNCC
UFFRJ

UFGRS

8 States
15 Institutions
34 Research Groups
25 CNPq Researchers

Research Network

RIO DE JANEIRO

RIO DE JANEIRO - RJ

UFRJ – FEDERAL UNIVERSITY OF RIO DE JANEIRO

INOFAR HEADQUARTERS FACULTY OF PHARMACY
- Laboratory of Evaluation and Synthesis of Bioactive Substances – LASSBio

SCHOOL OF CHEMISTRY
- Chemical Industry Information System – SIQUIM
- Luiz Alberto Coimbra Institute of Graduate Studies and Research in Engineering – COPPE

CARLOS CHAGAS FILHO BIOPHYSICS INSTITUTE
- Pulmonary Investigation Laboratory
- Molecular Parasitology Laboratory

BIOMEDICAL SCIENCES INSTITUTE
- Laboratory of Biochemical and Molecular Pharmacology
- Laboratory of Cardiovascular Pharmacology
- Laboratory of Muscular Excitation-Contraction Coupling

PROFESSOR PAULO DE GOES INSTITUTE OF MICROBIOLOGY
- Laboratory of Molecular Virology I
- Laboratory of Genetics and Immunology of Viral Infections

INSTITUTE OF CHEMISTRY
- Laboratory of Natural Products and Chemical Transformations
- Laboratory of Support to Technology Development - LADETEC

UERJ - UNIVERSITY OF THE STATE OF RIO DE JANEIRO

ROBERTO ALCANTARA GOMES INSTITUTE OF BIOLOGY
- Department of Pharmacology

FIOCRUZ – OSWALDO CRUZ FOUNDATION

OSWALDO CRUZ INSTITUTE
- Laboratory of Inflammation

NATIONAL SCHOOL OF PUBLIC HEALTH

SEROPÉDICA - RJ

UFRRJ – RURAL FEDERAL UNIVERSITY OF THE STATE OF RJ

INSTITUTE OF EXACT SCIENCES
- Department of Chemistry

PETRÓPOLIS - RJ

LNCC – NATIONAL LABORATORY OF SCIENTIFIC COMPUTATION
- Molecular Modeling of Biological Systems

MINAS GERAIS

BELO HORIZONTE – MG

UFMG – FEDERAL UNIVERSITY OF MINAS GERAIS

INSTITUTE OF EXACT SCIENCES, DEPARTMENT OF CHEMISTRY
- Innovation in Organic and Inorganic Compounds with Pharmacological Activity Group

ALFENAS – MG

UNIFAL – FEDERAL UNIVERSITY OF ALFENASS

DEPARTMENT OF PHARMACY
- Laboratory of Phytochemistry and Medicinal Chemistry

SÃO PAULO

ARARAQUARA – SP

UNESP – STATE UNIVERSITY OF SÃO PAULO

ARAQUARA INSTITUTE OF CHEMISTRY
- Bioassays, Biosynthesis, and Ecophysiology of Natural Products Nucleus - NUBBe

CAMPINAS – SP

UNICAMP – STATE UNIVERSITY OF CAMPINAS

INSTITUTE OF CHEMISTRY
- Laboratory of Synthetic Organic Chemistry

RIBEIRÃO PRETO – SP

USP – UNIVERSITY OF SÃO PAULO

FACULTY OF MEDICINE OF RIBEIRÃO PRETO
- Laboratory of Pain and Inflammation

RIO GRANDE DO SUL

PORTO ALEGRE - RS

UFRGS – FEDERAL UNIVERSITY OF RIO DE GRANDE DO SUL

FACULTY OF PHARMACY
- Laboratory of Experimental Psychopharmacology

CENTER OF BIOTECHNOLOGY – GENOTOX-ROYAL UNIT

LABORATORY OF GENOTOXICITY

Research Network

ALAGOAS

MACEIÓ – AL

UFAL – FEDERAL UNIVERSITY OF ALAGOAS
INSTITUTE OF BIOLOGICAL SCIENCES AND HEALTH
- Laboratory of Pharmacology and Immunity

CEARÁ

FORTALEZA – CE

UFC – FEDERAL UNIVERSITY OF CEARÁS
DEPARTMENT OF PHYSIOLOGY AND PHARMACOLOGY
- Clinical Pharmacology Unit
- Laboratory of Pharmacology of Inflammation and Cancer

PARAÍBA

JOÃO PESSOA – PB

UFPB – FEDERAL UNIVERSITY OF PARAÍBA
FACULTY OF PHARMACY
- Laboratory of Toxicology Assays

GOIÁS

GOIÂNIA - GO

UFG – FEDERAL UNIVERSITY OF GOIÁS
FACULTY OF PHARMACY
- Laboratory of Bioconversion
- Laboratory of Pharmacology and Cellular Toxicology
- Laboratory of Medicinal Pharmaceutical Chemistry
- Laboratory of Cardiovascular Pharmacology

Scientific Team

Leaders of Associated Laboratories

UFRJ
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CV-Lattes
Professor – CNPq 2

Angelo da Cunha Pinto
CV-Lattes
Professor – CNPq 1A

Carlos Alberto Manssour Fraga
CV-Lattes
Associate Professor – CNPq 1C

Eliezer J. Barreiro
CV-Lattes
Professor – CNPq 1A

Francisco Radler de Aquino Neto
CV-Lattes
Professor – CNPq 1A

François Germain Noel
CV-Lattes
Professor – CNPq 1C

Gisele Zapata Sudo
CV-Lattes
Associate Professor – CNPq 2

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CV-Lattes
Associate Professor – CNPq 1D

Lidia Moreira Lima
CV-Lattes
Professor – CNPq 2

Luciana Jesus da Costa
CV-Lattes
Professor

Patricia Dias Fernandes
CV-Lattes
Professor

Patricia Rieken Macedo Rocco
CV-Lattes
Associate Professor II – CNPq 1A

Ricardo de Andrade Medronho
CV-Lattes
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Roberto Takashi Sudo
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UERJ
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Professor – CNPq 1B

FIOCRUZ
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CV-Lattes
Researcher III – CNPq 2

Marco Aurelio Martins
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UFRRJ
Carlos Mauricio Rabello de Sant'Anna
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Associate Professor II – CNPq 2

LNCC
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CV-Lattes
Researcher

UFMG
Heloisa de Oliveira Beraldo
CV-Lattes
Professor – CNPq 1B

UNIFAL
Claudio Viegas Junior
CV-Lattes
Professor II

UNESP/ Araraquara
Vanderlan da Silva Bolzani
CV-Lattes
Professor – CNPq 1B

UNICAMP
Luiz Carlos Dias
CV-Lattes
Professor – CNPq 1B

USP/Ribeirão Preto
Fernando de Queiroz Cunha
CV-Lattes
Professor – CNPq 1A

UFRGS
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Science Director – Royal Institute – CNPq 1A

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UFPB
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CV-Lattes
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UFC
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CV-Lattes
Professor – CNPq 1B

Ronaldo de Albuquerque Ribeiro
CV-Lattes
Associate Professor – CNPq 1A

UFG
Ricardo Menegatti
CV-Lattes
Professor II

Valeria de Oliveira
CV-Lattes
Associate Professor I

Research Areas

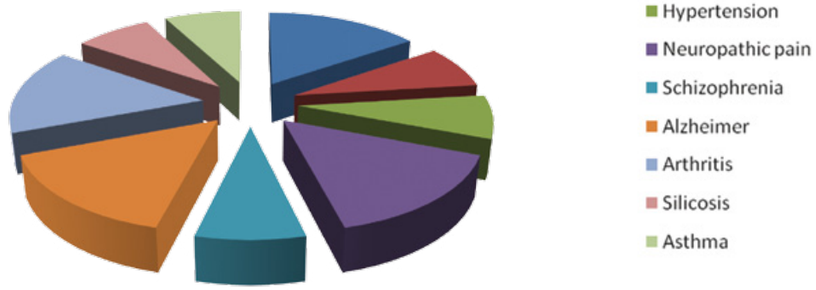
With the contribution of its entire research network, **INCT-INOFAR** develops subprojects in pharmaceutical innovation (radical innovation) and in generic medications (incremental innovation). In the area of radical innovation, the Institute has a goal of discovering an original substance, which produces a completely new medication. In the area of incremental innovation, the efforts are concentrated on the discovery of new synthetic routes for generic medications already available in the market as well as for those medications that have patents close to expiration.

For demanding competences in different areas of health like Medicinal Chemistry, Pharmacology, Toxicology, and Pharmaceutical Technology, as well as other specific fields of scientific knowledge, the innovation process in pharmaceuticals has multidisciplinary and pluriinstitutional characteristics, involving research groups renowned for their academic excellence, accredited by their earlier results and able to carry out successfully all the stages of the rational pharmaceuticals discovery process.

This team, made up of experts in Chemical, Biological, and Health Sciences, among which we can highlight expertises in Pharmacology, Toxicology, X-Ray Crystallography, Molecular Modeling, Organic Chemistry, Medicinal Chemistry, Natural Products Chemistry, Computational Chemistry, among other related areas, which favors the exchange between large research centers and emerging research groups. It contributes, as such, to reduce the regional imbalance in research activities and to enhance national expertise in a sector strategic to public health policy, as well as to increase scientific and technological production in the Midwest and Northeast regions of the country, improving the qualification at the graduate and undergraduate levels.

RESEARCH AREAS COVERED

- Inflammation;
- Asthma;
- Pain;
- Central Nervous System;
- Cardiovascular System;
- Chemotherapy: anticancer and antiparasitary



Current Subprojects

EARLY STAGE PROJECTS (07)

1. ***Evaluation of the mutagenic profile of bioactive substances that are candidates for pharmaceutical prototypes: a chain of innovation contribution in pharmaceuticals and medications.***
   Prof. Ana Luisa P. Miranda (UFRJ) - CV-Lattes

2. ***Theoretical Investigation of the Action Mechanism of Dialkylphosphorylhydrazones as Ribose 5-Phosphate Isomerase Enzyme Inhibitors of Trypanosoma cruzi and Plasmodium falciparum.***
   Prof. Carlos Mauricio R. de Sant'Anna (UFRRJ) - CV-Lattes

3. ***Triage of new replication inhibitors for the acquired human immunodeficiency virus Type 1 (HIV-1) from the LASSBio Chemical Library.***
   Prof. Luciana Jesus da Costa (UFRJ) - CV-Lattes

4. ***Evaluation of the antitumoral activity of new molecules planned structurally from the imatinib prototype.***
   Prof. Patricia Dias Fernandes (UFRJ) -CV-Lattes

5. ***Discovery of new neuraminidase inhibitors of the influenza virus.***
   Prof. Jose Nelson dos Santos Silva Couceiro (UFRJ) - CV-Lattes

6. ***Rational design of pharmaceuticals based on structures: applications and development of methods and program.***
   Prof. Laurent Emmanuel Dardenne – National Laboratory of Scientific Computation (LNCC), MCT - CV-Lattes

7. ***Prospection of Opportunities in New Generic and Innovative New Generic Medications.***
   Prof. Adelaide Maria de Souza Antunes (INPI) - CV-Lattes

INTERMEDIATE PROJECTS (07)

1. ***Benzaldehyde Semicarbazone(BS).***
   Prof. Heloisa de Oliveira Beraldo (UFMG) - CV-Lattes

2. ***Therapeutic potential of the new vasodilator compound (LASSBio 1289) in arterial and pulmonary hypertension.***
   Prof. Gisele Zapata Sudo (UFRJ) - CV-Lattes

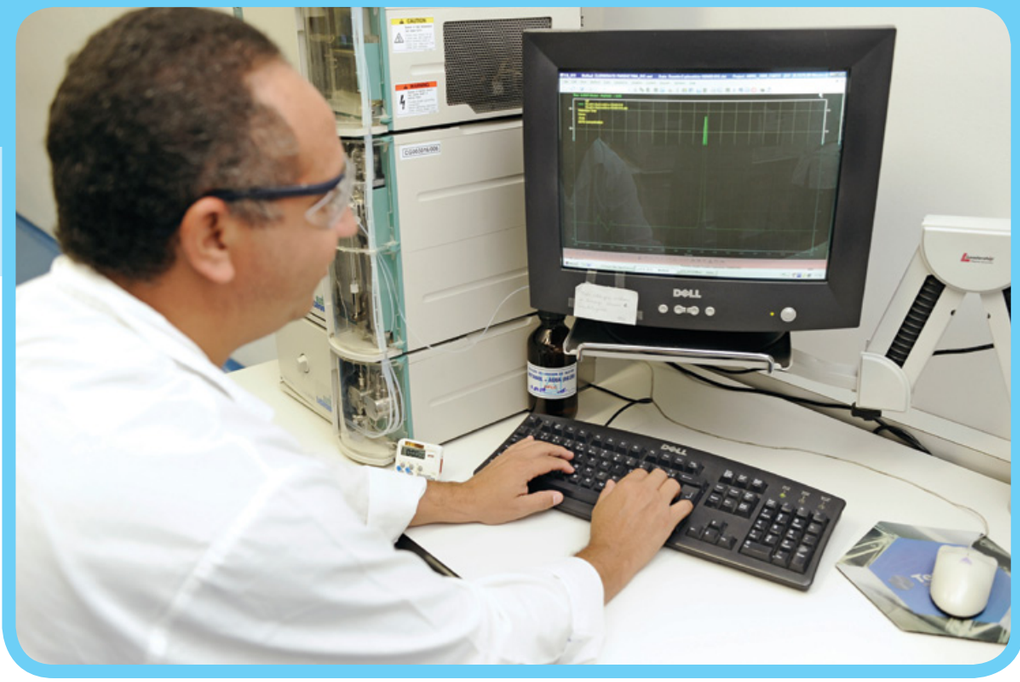
3. ***Pharmacological evaluation of new neuroactive Zolpidem derivatives.***
   Prof. Roberto Takashi Sudo (UFRJ) - CV-Lattes

4. ***"In silico" prediction and "in vitro" production through bioconversion of human metabolites of pharmaceutical prototype candidates.***
   Prof. Valeria de Oliveira (UFG) - CV-Lattes

5. ***Planning, synthesis and pharmacological evaluation of vectorized and self-organized neuroactive prototypes.***
   Prof. Ricardo Menegatti (UFG) - CV-Lattes

6. ***Planning, synthesis, structural characterization and pharmacological evaluation of new anti-inflammatory, anti-infective, and neuroactive pharmaceutical candidates.***
   Prof. Claudio Viegas Junior (UNIFAL-MG) - CV-Lattes

7. ***Evaluation of antiparasitary activity of a series of semicarbazone and hydrazine-n-acylhydrazone derivatives.***
   Prof. Magna Suzana Alexandre Moreira (UFAL) - CV-Lattes



ADVANCED PROJECTS (03)

1. ***Development of new anti-asthmatic pharmaceutical prototypes (LASSBio-596).***
   Prof. Patricia Rieken Macedo Rocco (UFRJ) - CV-Lattes
   Prof. Lidia Moreira Lima (UFRJ) - CV-Lattes

2. ***Study of functionalized n-phenylpiperazine derivatives as prototypes for the development of new atypical antipsychotics.***
   Prof. Stela Maris Kuze Rates (UFRGS) - CV-Lattes

3. ***Study of the potential anti-inflammatory effect of the LASSBio 897 compound, on silicosis and asthma models.***
   Prof. Patricia Machado Rodrigues e Silva (FIOCRUZ-RJ) - CV-Lattes
   Prof. Marco Aurelio Martins (FIOCRUZ-RJ) - CV-Lattes

GENERIC PHARMACEUTICALS (02)

1. ***Project for the synthesis of Atorvastatin in the National Science and Technology Institute of Drugs and Medicines INCT-INOFAR.***
   Prof. Luiz Carlos Dias (UNICAMP) - CV-Lattes

2. ***Synthesis of Sunitinib.***
   Prof. Angelo da Cunha Pinto (UFRJ) - CV-Lattes

Human Resources Qualification

Cooperating to improve the Brazilian skill set in the discovery/invention of new pharmaceuticals and medications, **INCT-INOFAR** invests heavily in the qualification of its personnel. Through a competent scientific Exchange program, it promotes the qualification at all academic levels: undergraduate, master's, doctoral, and post-doctoral, favoring and encouraging the mobility of graduate students (D > M) connected to the subprojects being studied, between the participating laboratories due to their specific expertise, so as to make it possible to meet all the benchmarks during the deadlines established for the project.

INCT-INOFAR is connected to Graduate Programs throughout the country through its associate researchers. Its positive contribution is reflected in the triennial evaluation of these Programs undertaken by the Coordination for the Improvement of Higher Level Personnel (CAPES). It should be noted that ca. nine programs indirectly connected to INCT-INOFAR have achieved levels of excellence (7, the maximum score, and 6).

(USP/RP) Graduate Program in BIOLOGICAL SCIENCES (PHARMACOLOGY) - M / D - **CAPES 7**

(UNICAMP) Graduate Program in CHEMISTRY – M / D - **CAPES 7**

(UFRJ) Graduate Program in CHEMISTRY – M / D – **CAPES 7**

(UNESP/ARAR) Graduate Program in CHEMISTRY - M / D- **CAPES 6**

(UERJ) Graduate Program in BIOSCIENCES – M/D - **CAPES 6**

(UFC) Graduate Program in PHARMACOLOGY – M/D - **CAPES 6**

(FIOCRUZ) Graduate Program in CELLULAR AND MOLLECULAR BIOLOGY - M / D – **CAPES 6**

(UFMG) Graduate Program in CHEMISTRY – M / D – **CAPES 6**

(UFRGS) Graduate Program in PHARMACEUTICAL SCIENCES - M / D - **CAPES 6**

(UFPB/J.P) Graduate Program in BIOACTIVE NATURAL AND SYNTHETIC PROGRAMS – M / D – **CAPES 5**

(UFRJ) Graduate Program in BIOLOGICAL SCIENCES (PHARMACOLOGY AND MEDICINAL CHEMISTRY) - M / D – **CAPES 4**

(UNIFAL) Graduate Program in MEDICINAL CHEMISTRY – **CAPES 4**

(UFRRJ) Graduate Program in CHEMISTRY – M / D – **CAPES 4**

(UFAL) Graduate Program in CHEMISTRY AND BIOTECHNOLOGY - M / D - **CAPES 4**

(UFAL) Graduate Program in HEALTH SCIENCES - M – **CAPES 3**

(UNIFAL) Graduate Program in PHARMACEUTICAL SCIENCES - M – **CAPES 3**

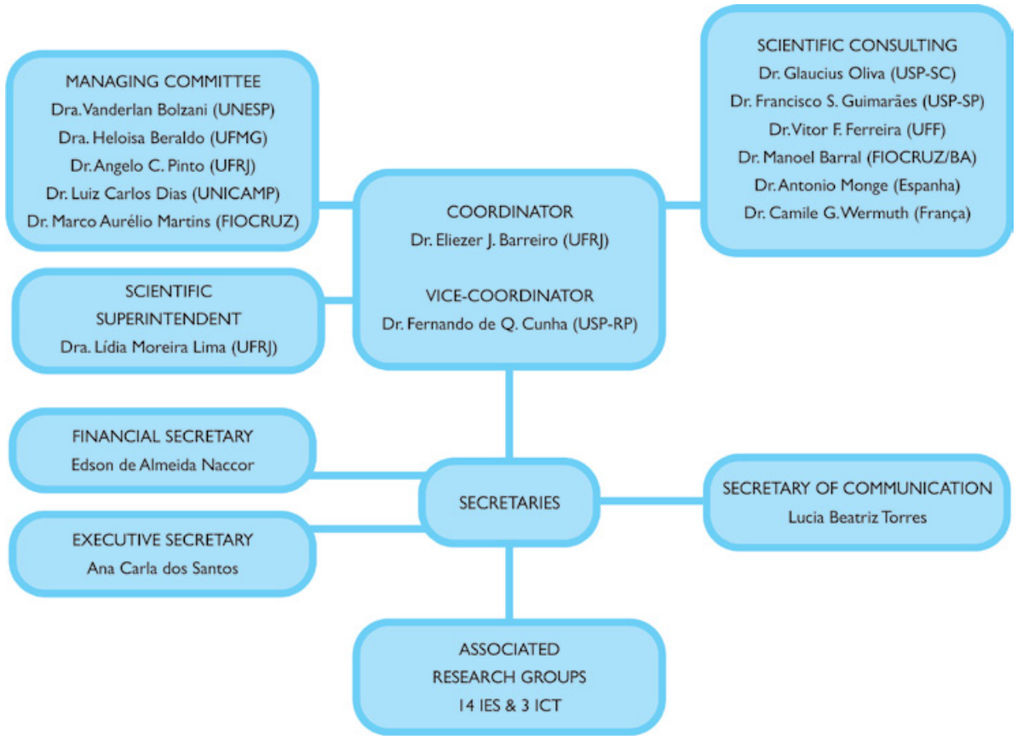
(UFG) Graduate Program in PHARMACEUTICAL SCIENCES - M - **CAPES 3**

Organizational Structure

The organizational structure of **INCT-INOFAR** is made up of a coordinator, a vice-coordinator, and a Managing and Follow-Up Committee (CGA). The CGA is a consulting and decision-making agency responsible for the strategic planning of the Institute, and it sanctions the decisions made by the coordinator and the vice-coordinator.

The Scientific Superintendence supports the CGA, acting in the technical evaluation of all projects developed by the Institute. **INCT-INOFAR** also has the participation, under confidentiality agreements, of specialist consultants who provide scientific assistance to the Institute by evaluating the projects being currently studied, aiming to optimize research activities.

Each associated research group is led by an expert responsible for the scientific interaction of his or her group with the other instances of the Institute. The Financial, Executive, and Media Relations Secretaries provide the necessary support to the full development of the Institute's research activities, and they are based at the Health Sciences Center of UFRJ, which serves as administrative headquarters for **INCT-INOFAR**.



ASSOCIATED COMPANIES

In Vitro Cells
www.invitrocells.com.br

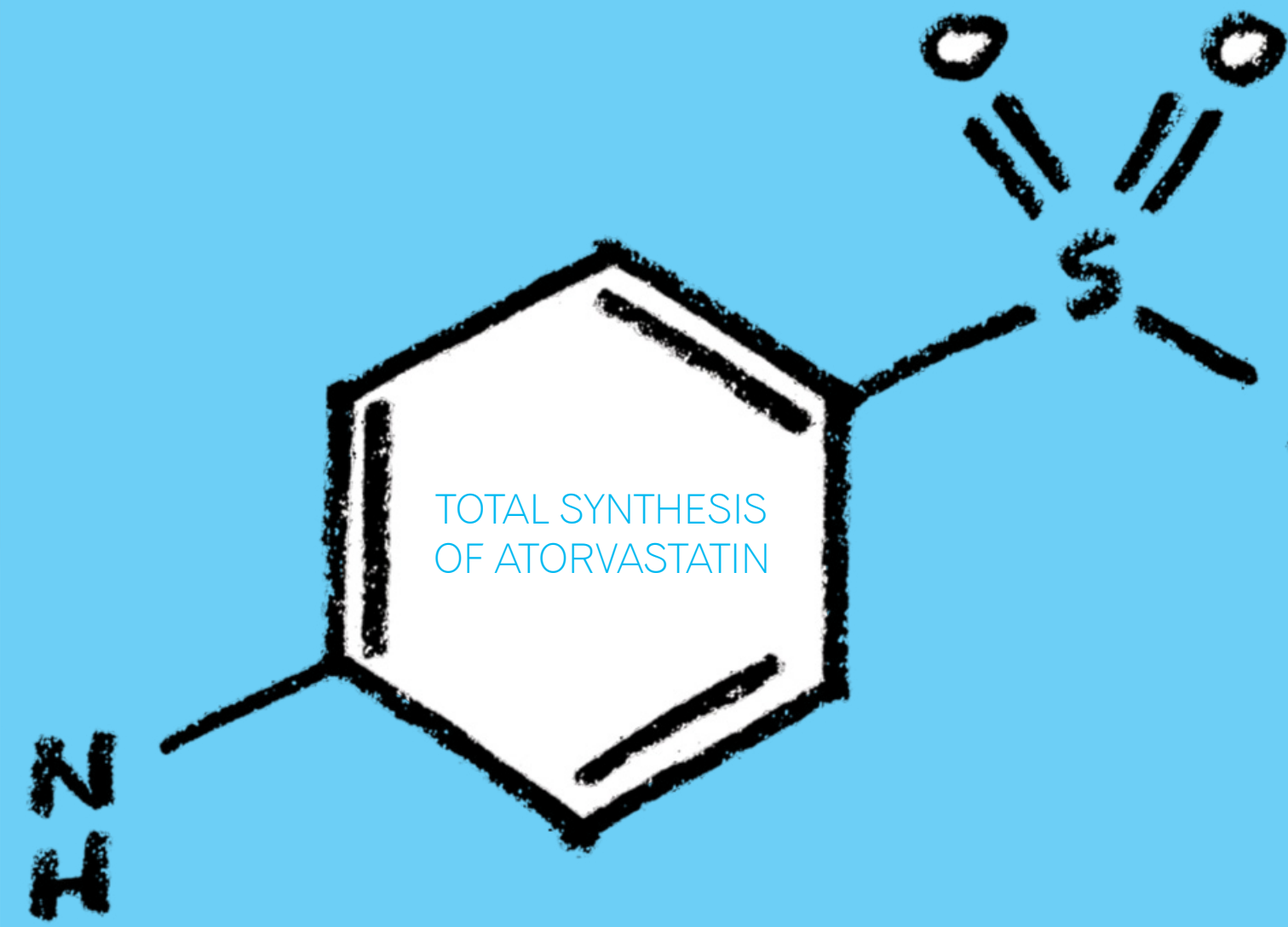
InVitro Cells – Toxicological Research S.A. is a technology-based company located at the Biominas Foundation (Belo Horizonte, MG). Its founders are professors at the Federal University of Minas Gerais in the areas of Toxicology and Biochemistry. The company is a partner of INOFAR in the conduction of *in vitro* assays for the evaluation of safety and efficacy of pharmaceutical candidates developed by the Institute.

Cristalia Laboratories Chemical and Pharmaceutical Products
www.2cristalia.com.br

Cristalia is a pharmaceutical company associated to **INCT-INOFAR**, capable of supporting the conduction, with onus, of the eventual stages of pharmacotechnical development of new compound-prototypes that reach this advanced staged of the chain of innovation in D & M. Under terms of confidentiality and non-disclosure, Cristalia will benefit, if it is interested, from the information on the projects being studied, by having right of refusal for adapting the technology developed by **INCT-INOFAR**. For transfer of technology, the UFRJ Innovation Agency and its equivalent in another **INCT-INOFAR** research institute will mediate a deal among all parties, including project financers.

Royal Institute (Instituto Royal)
www.institutoroyal.org.br

Toxicology is a very delicate stage that may absolve or condemn, for once, a molecule. **INCT-INOFAR** prioritizes genotoxicity and acute toxicology as early as possible in the chain of pharmaceutical innovation. To ensure that all the stages of pre-clinical toxicology are accredited in Good Laboratory Practices (BPL / GLP), **INCT-INOFAR** maintains a partnership with the Royal Institute, a result of the merger between two toxicology laboratories housed in different universities. The Genotox-Royal Institute, located at UFRGS, carries out genetic toxicity studies, while Unitox-Royal, located at the University of Santo Amaro (Unisa-SP), is responsible for testing toxicity in animals.



INCT-INOFAR
Annual Activities Report
2010

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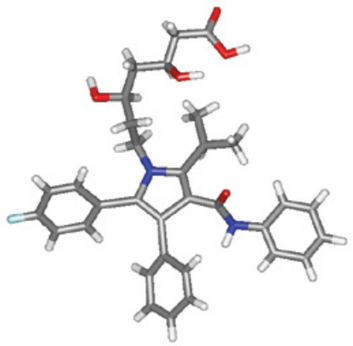
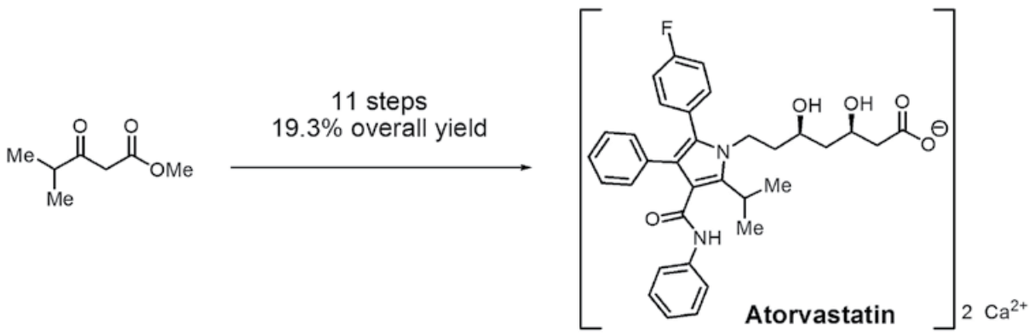
Total Synthesis of Atorvastatin

State University of Campinas - UNICAMP
National Institute of Science and Technology
in Drugs and Medicines **INCT-INOFAR**
Luiz Carlos Dias;
Eliezer J. Barreiro;
Adriano Siqueira Vieira

Atorvastatin is a drug in the statin class that is the most potent and widely used to lower cholesterol levels in blood, being marketed by Pfizer as Lipitor®. The drug inhibits the HMG-CoA reductase enzyme, reducing the amount of total cholesterol. The drug Lipitor®, totaled $ 13 billion in sales in 2009, being the best-selling drug worldwide. In Brazil alone, sales of Lipitor® made Pfizer approximately $ 400 million in 2009. Patent protection of atorvastatin in the U.S. is scheduled to expire in June 2011.



Our research group has developed a novel synthetic route for atorvastatin, the active ingredient in Lipitor®. The research was conducted in the laboratory of the Institute of Chemistry, State University of Campinas, supported by the National Institute of Science and Technology of Drugs and Medicines (**INCT-INOFAR**) and Cristalia Laboratory Chemicals and Pharmaceuticals.



We have re-investigated a number of chemical reactions described in earlier patents. After dozens of experiments, we introduced a series of incremental innovations in the process of obtaining a synthetic intermediate very important for the synthesis of atorvastatin. We were able to improve chemical yields of several steps employing milder reaction conditions. We reduced the amount of toxic solvents in a few steps, and eliminated them completely in others. We employed catalytic amounts of some reagents, among other news that cannot be detailed for reasons of confidentiality. From this intermediate, we introduced radical innovations, preparing atorvastatin by a synthetic method never before used, in excellent yields performing several steps in sequence without purifying the obtained products. Because of these improvements, the route developed is shorter, more efficient and cheaper, since the overall yield is higher than the original route from Pfizer and it employs lower-cost raw materials. Atorvastatin was prepared in 19.3% overall yield after 11 steps starting from readily available ketoester (**1**).

These innovations have great potential for implementation in an industrial scale. The patent application was sent to Inova Unicamp Innovation Agency, responsible for managing the intellectual property of the university. The patent application was filed in the National Institute of Industrial Property - INPI under protocol number: 018110015039 titled *Manufacturing process of atorvastatin calcium using new intermediates and atorvastatin thus obtained*.

Atorvastatin is a molecule with a high level of structural complexity. The synthesis of this very important molecule, using new synthetic strategy shows the excellence of scientists, and the research infra-structure in the country, and it would therefore be very useful for further investment in the area of generic drugs. The know-how of the INOFAR can be used for supporting the development of several active ingredients of drugs that can be helpful for the Public Health System - SUS, and the People's Pharmacy Program.

HIGHLIGHTS

INCT-INOFAR
Annual Activities Report
2010

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IL-17 mediates articular hypernociception in antigen-induced arthritis in mice

L. G. Pinto, T. M. Cunha, S. M. Vieira, H. P. Lemos, W. A. Verri Jr,
F. Q. Cunha, S. H. Ferreira

Pain (2010) *148*:247-56.
doi:10.1016/j.pain.2009.11.006

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by an increase in the infiltration of immune cells into the synovial membrane, cavity and periarticular tissues. An important cytokine in the physiopathology of RA is IL-17. IL-17 is secreted primarily by CD4+ T cells, traditionally known as Th17 cells, but is also secreted by CD8+ activated memory T cells, NKT cells and γδ lymphocytes. One of the most prevalent symptoms of arthritis is pain caused by the activation of sensitized (hypernociception) nociceptive fibers that supply the joint. In this study, we demonstrated that IL-17 participated in the genesis of articular hypernociception in a model of antigen-induced arthritis in mice. The hypernociceptive effect of IL-17 was reduced in TNFR1-/- mice and by pre-treatment with infliximab (anti-TNF antibody), a CXCR1/2 antagonist, or by an IL-1 receptor antagonist. Consistent with these findings, we found that IL-17 injection into joints increased the production of TNF-α, IL-1β and CXCL1/KC (Figure 1).

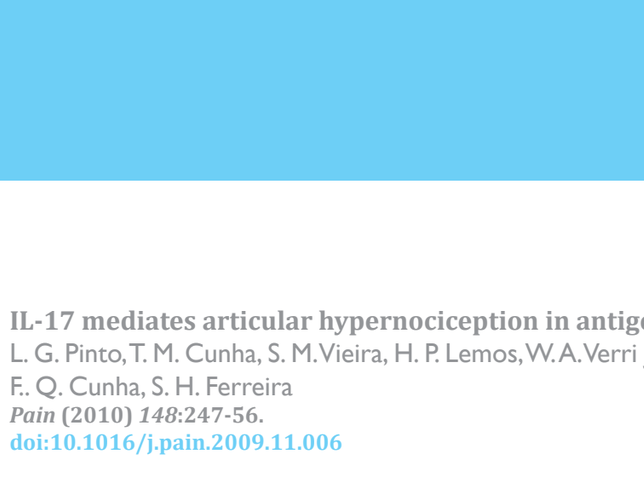


Figure 1 - Role of IL-17 in mBSA challenge-induced mechanical articular hypernociception. (A) mBSA-immunized mice were challenged i.a. with 10-90 µg of mBSA or 10 µl of saline. Articular hypernociception was evaluated 1-96 h following antigen challenge. **(B)** Articular hypernociception was evaluated 1- 24h after i.a. injection with either mBSA (30 µg) or saline in mBSA-immunized mice treated with a co-injection of IgG control (α-CTL) or α-IL-17 (2.25 µg/cavity) antibodies. At 24 hours, the mice were treated again with a second dose of antibodies. Articular hypernociception was evaluated 3 h following the second administration. **(C)** The concentration of IL-17 was determined at 3 and 12h after challenge. **(D)** mBSA-immunized mice were challenged i.a. with either 3-30 ng of IL-17 or 10 µl of saline and articular hypernociception was evaluated over a period of 7 hours. **(E)** mBSA-immunized wild type or TNFR1-/-mice were challenged i.a. with either IL-17 (30 ng per joint) or saline and articular hypernociception was evaluated 7h following challenge. **(F)** IL-17 (30 ng per joint) was injected into mice that were pretreated with infliximab, IL-1ra or DF-2156. Articular hypernociception was evaluated 7h after the challenge. The concentrations of TNF- α **(G)**, IL-1β **(H)**, and KC **(I)** in the knee joint injected with either 30 ng of IL-17 or saline in mBSA- immunized mice were determined at 1, 2, and 4 h after challenge. Data are means ± SEM (n=5) and representative of two independent experiments. *, $p < 0.05$ vs saline group; and #, $p < 0.05$ vs mBSA or IL-17 group.

Moreover, co-treatment of mBSA challenged mice with an antibody against IL-17 inhibited neutrophil recruitment. In agreement, intraarticular injection of IL-17 induced neutrophil migration, which was reduced by the pre-treatment with fucoidin, a leukocyte adhesion inhibitor (Figure 2).

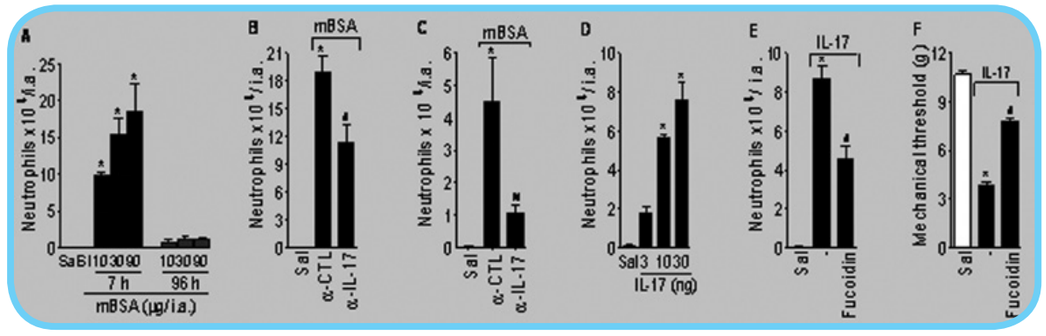


Figure 2- IL-17 mediates neutrophil recruitment to the knee joint of mice. Association of hypernociception and neutrophil migration. (A) Neutrophil recruitment from the articular cavity 7 and 96 h after i.a. injection of either mBSA (10- 90 µg) or saline. **(B and C)** mBSA-immunized mice were challenged i.a. with mBSA (30 µg) or saline and treated with a co-injection of IgG control (α-CTL) or anti-IL-17 (2.25 µg/cavity) antibodies. **(B)** Neutrophil migration was evaluated 7h after challenge. **(C)** Mice were treated with a second round antibodies and neutrophil recruitment was evaluated 3h after antibody treatment. **(D)** Neutrophil recruitment was evaluated 7h after i.a. injection of either IL-17 (3-30 ng per joint) or saline in mBSA-immunized mice. Neutrophil migration **(E)** and articular hypernociception **(F)** in mice challenged with IL-17 (30 ng per joint) and pretreated with fucoidin were evaluated 7h after antigen challenge. Data are means ± SEM (n=5), representative of two independent experiments. *, $p < 0.05$ vs saline group; and #, $p < 0.05$ vs mBSA or IL-17 group.

It is broadly accepted that articular hypernociception results mainly from the direct and indirect effects of inflammatory mediators on the sensitization (increase of excitability) of primary nociceptive fibers that innervate the inflamed joints. Prostaglandins and sympathetic amines are the key mediators of this process and their release is generally stimulated by the release of cytokine cascades, a process that appears to be neutrophil-dependent. Treatment with indomethacin (cyclooxygenase inhibitor) or guanethidine (sympathetic blocker) also inhibited IL-17-induced hypernociception. IL-17 injection also increased PGE2 production and COX-2 mRNA expression in the synovial membrane (Figure 3).

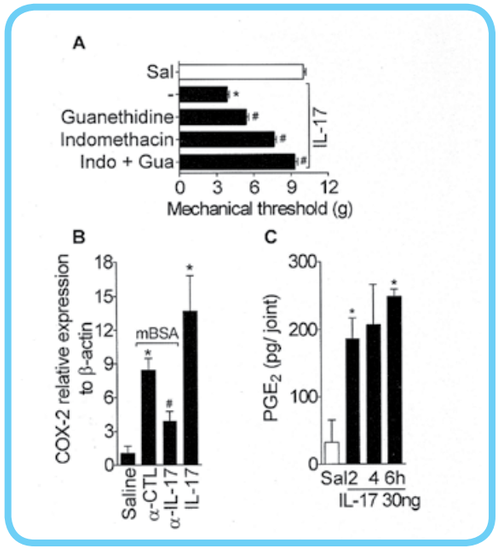
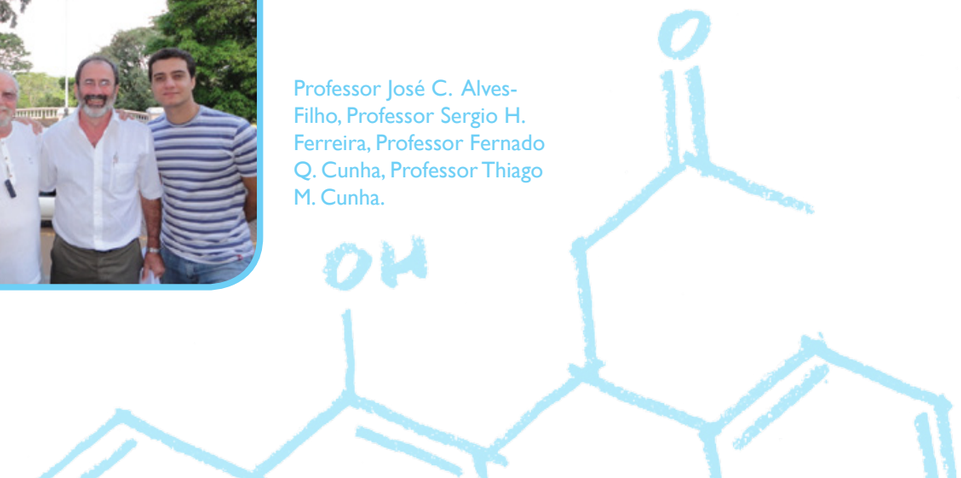


Figure 3 - Role of prostanoids and sympathomimetic amines in IL-17-induced mechanical articular hypernociception in the knee joint of mice. (A) Articular hypernociception induced by IL-17 (30ng/ cavity) in mBSA-immunized mice pretreated with indomethacin, guanethidine or indomethacin plus guanethidine. The articular hypernociception was determined 7h after challenge. **(B)** mBSA-immunized mice were challenged i.a. with either saline, IL-17 (30 ng) or mBSA (30 μg) and treated with co-injection of IgG control (α-CTL) or anti-IL-17 antibodies. After 1.5h, synovial membranes were collected and analyzed for COX-2 mRNA expression by PCR. The gene expression was normalized to β-actin expression. **(C)** The knee joints of mBSA-immunized mice were collected 2 and 6h after challenge i.a. with IL-17 and assayed for PGE2 levels. Results are mean ± SEM (n=4), representative of two independent experiments. *,$p < 0.05$, compared with saline group; and # ,$p < 0.05$, compared with mBSA or IL-17 group.

These results suggest that IL-17 is a novel pro-nociceptive cytokine in RA whose effect depends on both neutrophil migration and various pro-inflammatory mediators such as TNF-α, IL-1β, CXCR1/2 chemokines ligands, prostaglandins and sympathetic amines. Therefore, it is reasonable to propose IL-17 targeting therapies to control this important RA symptom.

Professor José C. Alves-Filho, Professor Sergio H. Ferreira, Professor Fernado Q. Cunha, Professor Thiago M. Cunha.



LASSBio-294, A Compound With Inotropic and Lusitropic Activity, Decreases Cardiac Remodeling and Improves Ca2+ Influx Into Sarcoplasmic Reticulum After Myocardial Infarction

D. G. Costa , J. C. Silva, A. E. Kummerle, R. T. Sudo, S. S. Landgraf, C. Caruso-Neves, C. A. M. Fraga, E. J. Barreiro, and G. Zapata-Sudo

Journal of Hypertension (2010) 23: 1220-1227.
doi:10.1038/ajh.2010.157

Myocardial infarction (MI) induces many alterations in the cardiovascular system that progressively compromise regular blood pumping and tissue perfusion. MI is normally associated with the development of cardiac cell necrosis, fibrotic tissue, heart hypertrophy and dilatation of the ventricles, which together lead to heart remodeling. Chronic activation of mechanical, molecular, and neurohumoral responses to hypoxia can lead to adaptations that frequently induce heart failure (HF). The primary characteristics of HF include impaired ventricular filling, pulmonary edema, and reduced exercise tolerance. The need for novel therapeutic strategies to prevent cardiac remodeling subsequent to MI is great, and improvement of the dysfunction of sarcoplasmic reticulum-calcium ATPase (SERCA2) in cardiac muscle from MI animals could be benefitial and result in positive inotropism and lusitropism.

Recently, several new bioactive compounds of the *N*-acylhydrazone class were developed and the replacement of the phenyl ring attached to the imine moiety by the isosteric 2-thienyl ring originally resulted in the design of 3,4-methylenedioxybenzoyl-2-thienylhydrazone, named LASSBio-294 (Figure 1).

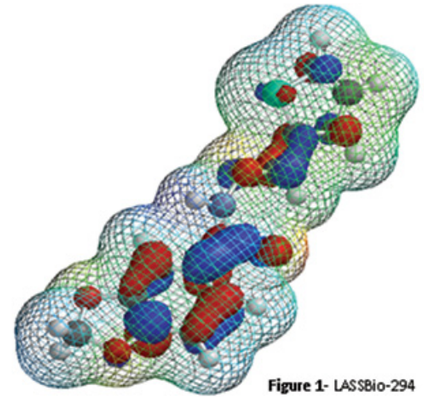


Figure 1- LASSBio-294

LASSBio-294 was described as a potent positive cardiac inotropic agent, whose activity was related to an increased accumulation of Ca2+ into the sarcoplasmic reticulum (SR). The effects of chronic administration of LASSBio-294 have not yet been determined in rats subjected to experimental MI. Herein, we investigated whether daily treatment with LASSBio-294 interfered with cardiac remodeling, Ca2+ homeostasis, and hemodynamic disturbances associated with MI.

Experimental MI was induced as follows: Under sevoflurane anesthesia, rats were subjected to ligation of the anterior descending coronary artery. In the sham-operated group, the same procedure was conducted, but without artery occlusion. Rats were randomly divided into sham-operated and MI groups, and each group was further divided into two additional subgroups: treatment with vehicle (dimethyl sulfoxide (DMSO)) or treatment with LASSBio-294 (2 mg/kg) during 4 weeks (Figure 2).

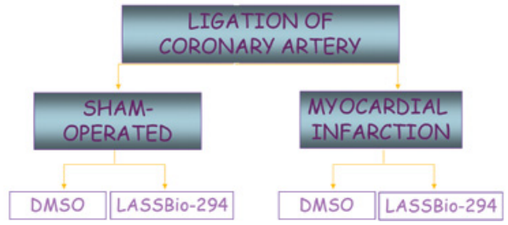


Figure 2- Experimental groups

Hematoxylin and eosin-stained sections are shown in Figure 3A. Marked cell infiltration with increased nuclear density was observed in the myocardium of MI-vehicle group (Figure 3A) compared to sham-vehicle group. Administration of LASSBio-294 after MI completely prevented the cellular infiltration.

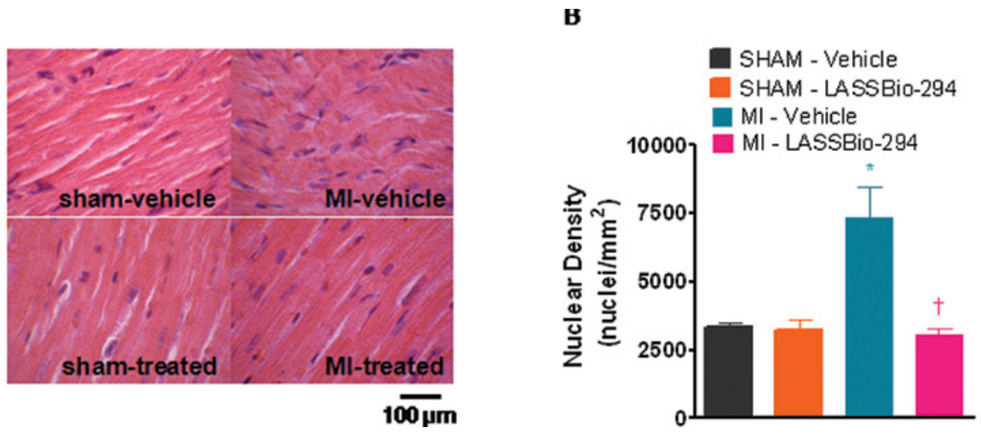


Figure 3 Pathological analysis of the left ventricles treated with vehicleor LASSBio-294. (**A**) Representative micrograph of hematoxylin and eosin staining and (**B**) data for total cell density. $n = 10$ animals per group. $^*P < 0.05$ compared to sham-vehicle and †compared to MI-vehicle. LASSBio-294, 3,4-methylenedioxybenzoyl-2-thienylhydrazone; MI, myocardial infarction.

Marked increase in the collagen volume fraction area was observed in the MI-vehicle group. LASSBio-294 significantly reduced the volume fraction, resulting in the decreased deposit of collagen. An elevation in the heart weight/body weight index was observed in MI-vehicle group that was partially reduced after treatment with LASSBio-294 at the end of the 4-week treatment.

Administration of LASSBio-294 led to dramatically reduced nuclear density and collagen volume, indicating that treatment was associated with decreased immune system activation. As with other anti-inflammatory drugs, LASSBio-294 may decrease inflammation and cardiac fibrosis by regulating inflammatory mediators.

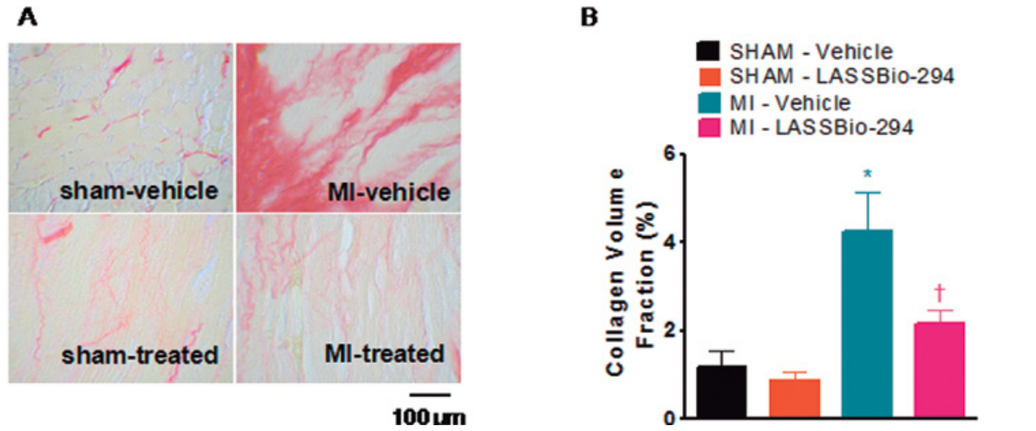


Figure 4- Collagen volume analysis of the left ventricle treated with vehicle or LASSBio-294. (**A**) Representative micrograph of picrosirius red staining and (**B**) data of volume collagen fraction area. $n = 10$ animals per group. $^*P < 0.05$ compared to sham-vehicle and † compared to MI-vehicle.

SR-Ca2+ loading was evaluated based on the contractile response induced by caffeine with increasing periods of SR-loading cycle. Figure 5 shows the caffeine response relative to the loading time. Caffeine-induced contraction increased as a function of loading time in the sham-vehicle group. MI reduced SR-Ca2+ accumulation because the caffeine-induced contraction was smaller than in the sham-vehicle group. Treatment with LASSBio-294 significantly increased the amplitude of the caffeine response.

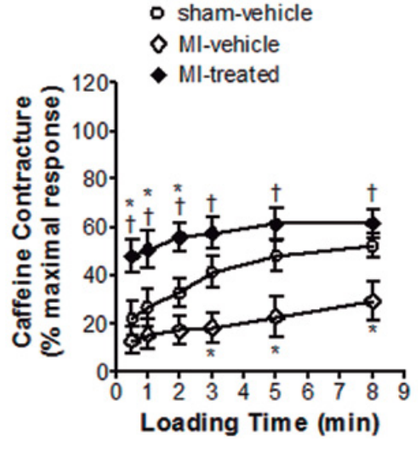


Figure 5 - SR-Ca2+ uptake on saponin-skinned cardiac cells. Caffeine-induced contractures obtained with exposure to pCa 7.4 during different periods (0.5–8 min) of SR loading. Data were expressed relative to the maximal contractile response of fibers obtained after exposure to a high concentration of Ca2+ (pCa 4.8 = 15.85 µmol/l Ca2+). $n = 6–8$ animals per group. $^*P < 0.05$ compared to sham-vehicle and †compared to MI-vehicle. pCa = −log [Ca2+]. SR, sarcoplasmic reticulum.

SERCA2a expression in left ventricle homogenates from different experimental groups was analyzed by immunoblotting. SERCA2a expression decreased by 47% in MI-vehicle group relative to the age-matched sham-vehicle group. In contrast, SERCA2a expression in the MI-treated group increased by 66 and 210% when compared to sham-vehicle and MI-vehicle groups, respectively (Figure 6).

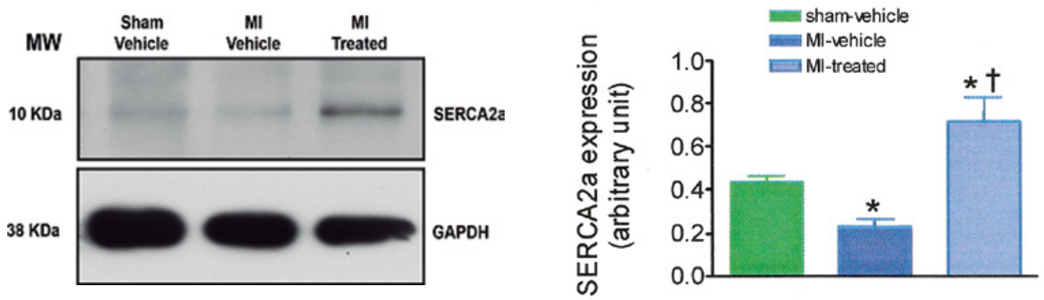


Figure 6- Effect of LASSBio-294 treatment on the expression of SERCA2a in infarcted animals. Homogenates prepared from left ventricular tissue of rats 4 weeks after MI surgery were subjected to western blot analysis. The obtained band intensities were normalized by GAPDH expression. Aliquots of 50 µg of protein were loaded per lane. *n* = 5 animals per group. The results are expressed as mean + SE. *$P < 0.05$ compared to sham-vehicle and †compared to MI-vehicle. LASSBio-294, 3,4-methylenedioxybenzoyl-2-thienylhydrazone; MI, myocardial infarction; SERCA2a, sarcoplasmic reticulum-calcium ATPase 2a; MW, molecular weight.

One of the most important processes that regulates cardiomyocyte relaxation is the activation of SERCA2a. This protein induces Ca2+ uptake from the cytosol to the SR lumen, thereby activating cell relaxation which is one of the first Ca2+ handling processes impaired by MI. The faster SERCA activity and the greater its density, the more intense is the improvement of cardiac function after MI. LASSBio-294 enhances SR-Ca2+ uptake on cardiac fibers through the increased density of SERCA2a which could increase intracellular Ca2+ mobilization by improving SERCA expression. Then, LASSBio-294 is considered as a distinct positive cardioinotropic agent, which differs from other drugs that act to elevate cytosolic Ca2+ levels. This feature is extremely important in the treatment of HF, because it reduces cardiotoxicity and prevents cardiac dysfunction.

We further evaluated the effect of LASSBio-294 administration on cardiac remodeling, through the determination of its effectiveness on ameliorating hemodynamic parameters. Our data demonstrated that significant alterations were observed in left ventricle (LV) end diastolic pressure (EDP) and LV d*P*/dtmin after MI. Administration of LASSBio-294 returned the LV EDP to normal values and enhanced lusitropism.

	sham-vehicle	MI-vehicle	MI-treated
Body wt (g)	286.3 ± 11.6	278.5 ± 7.9	269.0 ± 8.0
Heart wt/ Body wt (mg/g)	4.5 ± 0.2	6.8 ± 0.3*	5.7 ± 0.2*#
Heart rate (bpm)	335 ± 15	315 ± 21	346 ± 12
Mean blood pressure(mm Hg)	94. 3 ± 6.2	88.2 ± 5.1	89.6 ± 12.1
LV ESP (mm Hg)	110 ± 7.7	95.2 ± 5.2	99.9 ± 5.8
dP/dt_{max} (mm Hg/s)	5349.6 ± 299.8	2218.9 ± 165.9*	6812.1 ± 11804.5#
LV EDP (mm Hg)	4.5 ± 3.6	16.4 ± 2.5*	9.0 ± 2.2#
dP/dt_{min} (mm Hg/s)	-3765.7 ± 678.6	-1018.1 ± 373.1*	-4464.8 ± 355.1#

LV ESP, left ventricular end-sistolic pressure; LV EDP, left ventricular end-diastolic pressure; wt, weight. n = 15 animals * $P < 0.05$ compared to sham-vehicle # compared to MI-vehicle.

In conclusion, cardiac remodeling and diastolic disturbances observed at 4 weeks after MI could be restored by treatment with LASSBio-294. Treatment with LASSBio-294 prevented cell infiltration, collagen development, and increased SR-Ca2+ accumulation and Ca2+ sensitivity of contractile proteins after MI.

Prof. Gisele Zapata-Sudo, Prof. Roberto Takashi Sudo and their research team

Bone marrow-derived mononuclear cell therapy in experimental pulmonary and extrapulmonary acute lung injury

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doi: 10.1097/CCM.0b013e3181e796d2

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are common causes of morbidity and mortality in the intensive care unit. Hastening the repair process and attenuating both the inflammatory and fibrogenic responses are thought to be important aspects in the effort to improve ALI/ARDS management.

Source: http://www.lawsonresearch.com/lung/images/lungs_1.jpg

There are various triggers for ALI/ARDS, and differences in the initial insult combined with underlying conditions may result in the activation of different inflammatory mechanisms. In pulmonary ALI, the primary structure injured is the alveolar epithelium, while in extrapulmonary ALI endothelial cells are the first target of damage. Therefore, considering that the pathophysiology of early ALI/ARDS differs according to the type of primary insult, we hypothesized that bone marrow-derived mononuclear cell (BMDMC) therapy might act differently on lung and distal organs in experimental models of pulmonary (p) or extrapulmonary (exp) ALI with similar mechanical compromise at the early phase of the lesion.

ALI animals received *Escherichia coli* lipopolysaccharide intratracheally (40 µg, ALIp) or intraperitoneally (400 µg, ALIexp). Six hours after lipopolysaccharide administration, ALIp and ALIexp animals were further randomized into subgroups receiving saline (0.05 mL) or BMDMC (2x106) intravenously.

ALI animals received *Escherichia coli* lipopolysaccharide intratracheally (40 µg, ALIp) or intraperitoneally (400 µg, ALIexp). Six hours after lipopolysaccharide administration, ALIp and ALIexp animals were further randomized into subgroups receiving saline (0.05 mL) or BMDMC (2x106) intravenously.

At day 7, BMDMC led to: 1) increase in survival rate (Figure 1) ; 2) reduction in static lung elastance (Figure 2), alveolar collapse, and bronchoalveolar lavage fluid cellularity (higher in ALIexp than ALIp); 3) decrease in collagen fiber content (Figure 2), cell apoptosis in lung, kidney, and liver, levels of interleukin (IL)-6, KC (murine IL-8 homolog), and IL-10 in bronchoalveolar lavage fluid (Figure 3), and mRNA expression of insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), and transforming growth factor (TGF)-b in both groups (Figure 4), as well as repair of basement membrane, epithelium and endothelium regardless of ALI etiology (Figure 5); 4) increase in vascular endothelial growth factor levels in bronchoalveolar lavage fluid and mRNA expression in lung tissue in both ALI groups; and 5) increase in number of green fluorescent protein positive cells in lung, kidney, and liver in ALIexp (Figure 6).

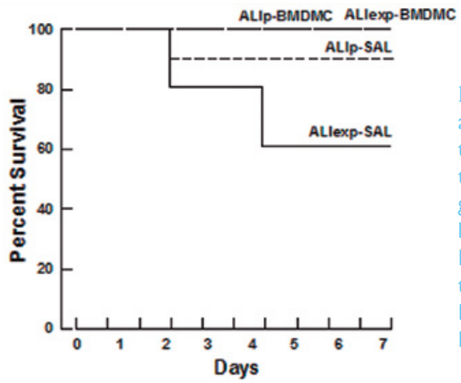

Figure 1. Kaplan-Meier survival curves of animals classified according to BMDMC or SAL treatment in ALIp and ALIexp. After BMDMC therapy, survival rate was 100% in both groups. Note that BMDMC therapy led to a better response in ALIexp compared to ALIp. Data represent percentage survival of saline-treated mice (ALIp,n=8 and ALIexp,n=12) and BMDMC-treated mice (n=7/group) 6 h after LPS induced lung injury.

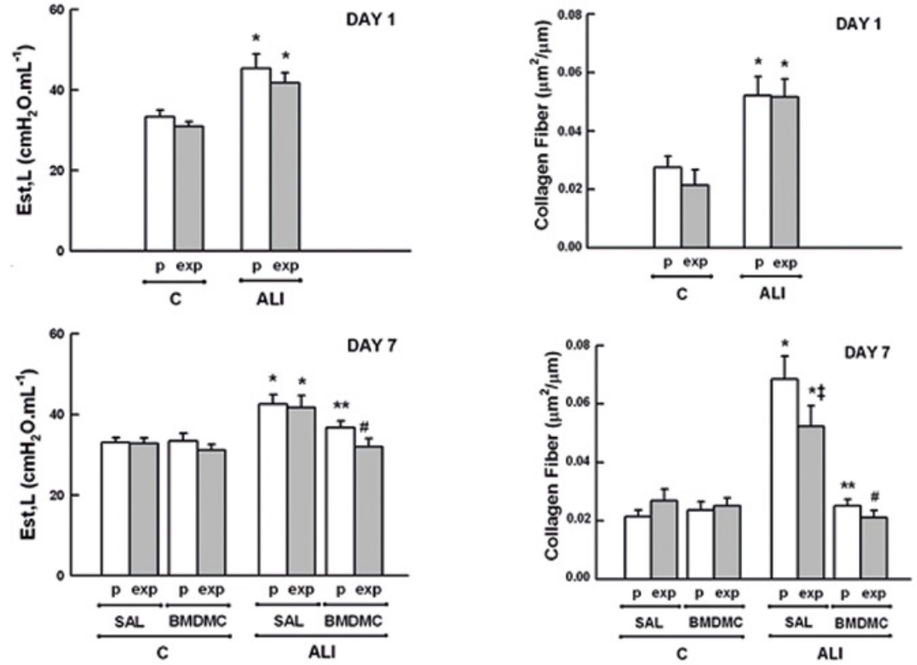

Figure 2. Static lung elastance (*Est,L*) (*left panels*) and collagen fiber content (*right panels*) at days 1 (*upper panel*) and 7 (*lower panel*). Values are mean ± SD of seven animals in each group (10 determinations per animal). *Significantly different from group C ($p < 0.05$). **ALIp-BMDMC *vs* ALIp-SAL ($p < 0.05$). #ALIexp-BMDMC *vs* ALIexp-SAL ($p < 0.05$). ‡ ALIexp-SAL *vs* ALIp-SAL ($p < 0.05$),† ALIexp-BMDMC *vs* ALIp-BMDMC ($p < 0.05$).

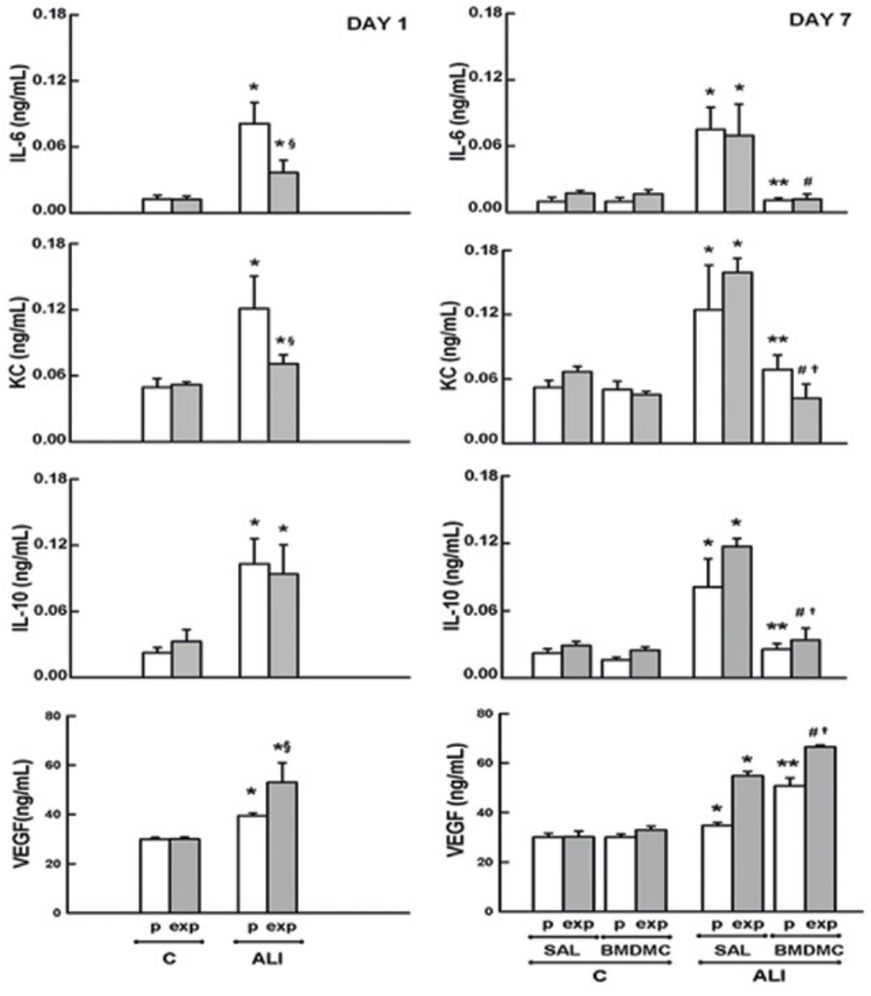

Figure 3. Interleukin (IL)-6, KC (murine IL-8 homolog), IL-10, and vascular endothelial growth factor (VEGF) levels in bronchoalveolar lavage fluid at days 1 (*left panels*) and 7 (*right panels*). C: control, ALI: acute lung injury, p: pulmonary, exp: extrapulmonary, SAL: saline, BMDMC: bone marrow-derived mononuclear cell therapy. Values are means ± SD of 5 animals in each group. *Significantly different from group C ($p < 0.05$). §ALIp *vs* ALIexp ($p<0.05$). **ALIp-BMDMC *vs* ALIp-SAL ($p < 0.05$). #ALIexp-BMDMC *vs* ALIexp-SAL ($p < 0.05$). †ALIexp-BMDMC *vs* ALIp-BMDMC ($p < 0.05$).

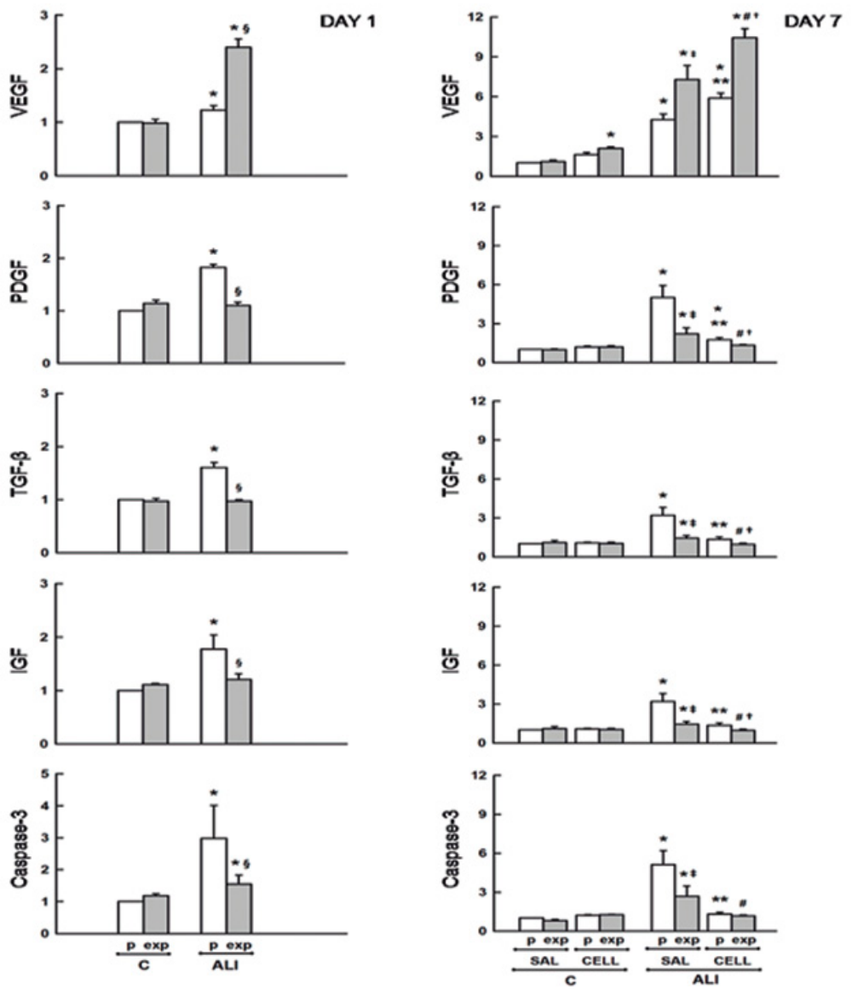

Figure 4. Real-time polymerase chain reaction analysis of VEGF: *vascular endothelial growth factor; TGF-β: transforming growth factor-beta;* PDGF: platelet-derived growth factor; IGF: insulin growth factor; and caspase-3 mRNA expressions of mouse lung tissue. Data are normalized to GAPDH expression. C: control, ALI: acute lung injury, p: pulmonary, exp: extrapulmonary, SAL: saline, BMDMC: bone marrow-derived mononuclear cell therapy. The *y* axis represents fold increase compared with Cp. Values are means ± SD of 4 animals in each group. *Significantly different from group C ($p < 0.05$). **ALIp-BMDMC *vs* ALIp-SAL ($p < 0.05$). #ALIexp-BMDMC *vs* ALIexp-SAL ($p < 0.05$). ‡ALIexp-SAL *vs* ALIp-SAL ($p < 0.05$). †ALIexp-BMDMC *vs* ALIp-BMDMC ($p < 0.05$).

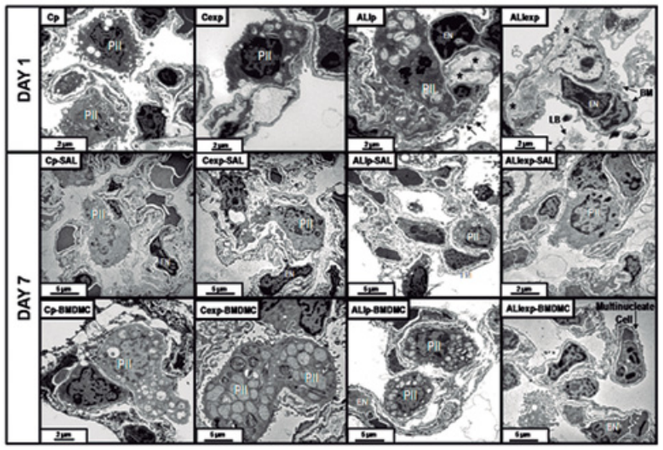

Figure 5. Electron microscopy of lung parenchyma at days 1 (*first row*) and 7 (*second and third panels*). C: control, ALI: acute lung injury, p: pulmonary, exp: extrapulmonary, SAL: saline, BMDMC: bone marrow-derived mononuclear cell therapy. Type II cell (PII) as well as alveolar capillary membrane were damaged in all ALI groups. After BMDMC therapy, fusion of type II cells was observed associated with multinucleate cells with no characteristic phenotype. Furthermore, repair of basement membrane is seen in both ALI groups. Photomicrographs are representative of data obtained from lung sections derived from five animals.

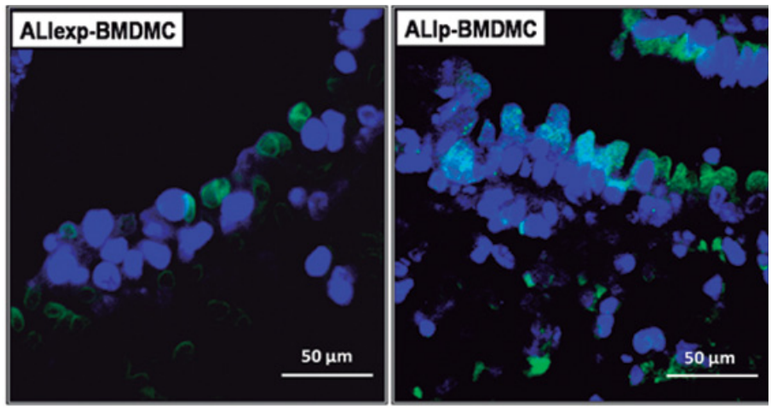

Figure 6. Confocal microscopy of lung parenchyma examined at day 7 in extrapulmonary (ALIexp-BMDMC) and pulmonary (ALIp-BMDMC) acute lung injury treated with BMDMC from GFP mice. Note that few GFP+ cells (green) were present in the lung parenchyma in both ALI groups.

In conclusion, BMDMC therapy was effective at modulating the inflammatory and fibrogenic processes in both ALI models; however, survival and lung mechanics and histology improved more in ALIexp. These changes may be attributed to paracrine effects balancing pro- and anti-inflammatory cytokines and growth factors, since a small degree of pulmonary BMDMC engraftment was observed.

2-Acetylpyridine thiosemicarbazones: cytotoxic activity in nanomolar doses against malignant gliomas

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Thiosemicarbazones are an interesting class of compounds with wide pharmacological versatility and applications as antimicrobial, antiviral and antitumor agents. The antitumor activity of α(N)-heterocyclic thiosemicarbazones has been extensively investigated. This search led to the onset of clinical studies of 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP, Triapine®).

The mechanism of action of α(N)-heterocyclic thiosemicarbazones involves inhibition of iron-dependent ribonucleoside diphosphate reductase (RDR), a rate-limiting enzyme in DNA syntheses, which mediates the conversion of ribonucleotides into desoxiribonucleotides.

The cytotoxic activity of thiosemicarbazones and their metal complexes against a variety of human solid tumor cell lines and against leukemia cells has been demonstrated by other authors and by our group. We demonstrated that gallium(III) and tin(IV) complexes with thiosemicarbazones present cytotoxicity against malignant glioma and that palladium(II) and antimony(III) complexes with thiosemicarbazones are cytotoxic to human leukemia cell lineages.

In the present work 2-acetylpyridine *N*(4)-phenyl thiosemicarbazone (H2Ac4Ph) and its *N*(4)-*ortho*-tolyl (H2Ac4oT), *N*(4)-*meta*-tolyl (H2Ac4mT), *N*(4)-*para*-tolyl (H2Ac4pT), *N*(4)-*ortho*-chlorophenyl (H2Ac4oClPh), *N*(4)-*meta*-chlorophenyl (H2Ac4mClPh) and *N*(4)-*para*-chlorophenyl (H2Ac4pClPh) derivatives were assayed for their cytotoxic activity against malignant glioma cells. We used the rat glioma RT2 cells, which express wild-type p53 protein and the human glioma T98 cells, expressing mutant p53. Apoptosis of glioma cells is triggered primarily by a p53 pathway. Cells with mutant or absent p53 are less sensitive than cells with wild-type p53 to the majority of clinically used anticancer agents.

Cytotoxic activity against malignant RT2 and T98 glioma cells

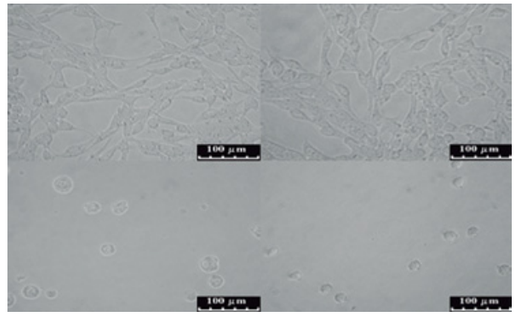

Figure. 1 RT2 (left) and T98 (right) cells treated with H2Ac4oClPh (10−6 mol L−1, bottom) or diluent (top) in culture dishes. After 48 h the dishes were observed under phase contrast and membrane morphology was photographed. Characteristics of apoptosis are clearly visible: blebs, rounding cells (magnification ×200).

Thiosemicarbazones induce membrane changes characteristics of apoptosis. After exposure to the compounds retraction of the cytoplasmatic expansions, leading to round shaped cells, cell shrinkage and blebs formation were noticed. Reduction of the number of cells after treatment was also observed (Fig. 1).

Thiosemicarbazones induce nuclear changes characteristics of apoptosis

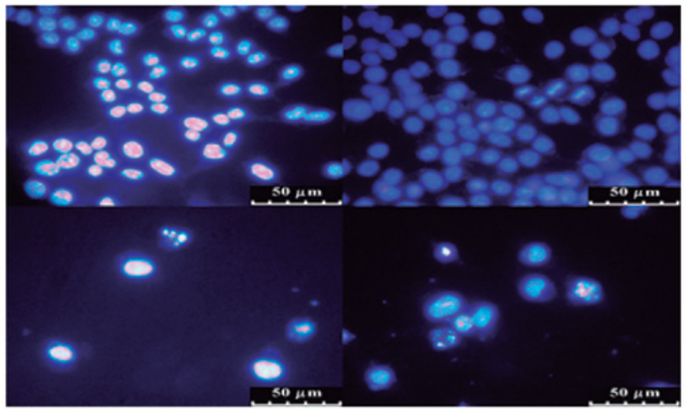

Figure 2 RT2 (left) and T98 (right) cells were treated with H2Ac4oClPh (10−6 mol L−1, bottom) or diluent (top). After 48 h cells were fixed and stained with DAPI. Chromatin condensation and nuclear fragmentation can be observed (Magnification ×400).

Triggering of apoptosis induces DNA fragmentation through the activation of specific DNA endonucleases. Activation of nucleases can be evidenced through the use of DNA staining with 4′,6′-diamidino-2-phenylindole (DAPI), which detects fragmented and condensed DNA. No DNA fragmentation was observed in the untreated cells, but following exposure to the thiosemicarbazones, cells exhibited extensive DNA fragmentation (Fig.2).

The concentrations of compounds which kill 50% of RT2 and T98 glioma cells (IC50) are listed in Table 1, together with their hemolytic activity.

Compound	IC_{50} (µmol L^{-1})		Haemolytic activity (mol L^{-1})
	T98	RT2	
H2Ac4oT	0.034 ± 0.003	0.014 ± 0.007	>10−3
H2Ac4mT	0.050 ± 0.018	0.024 ± 0.012	>10−3
H2Ac4pT	0.037 ± 0.003	0.017 ± 0.011	>10−3
H2Ac4Ph	0.0068 ± 0.0008	0.0014 ± 0.0008	>10−3
H2Ac4oClPh	0.0011 ± 0.00096	0.0014 ± 0.0003	>10−3
H2Ac4mClPh	0.0010 ± 0.0004	0.009 ± 0.003	>10−3
H2Ac4pClPh	0.0059 ± 0.0008	0.0037 ± 0.0002	>10−3
Cisplatin	17 ± 1	5 ± 3	>10−3

All thiosemicarbazones were highly active with IC50 values in the nanomolar range against both RT2 and T98 cells. All were able to induce cell death by apoptosis. The compounds presented haemolytic activity with much higher IC50 values (>10−3 M).

SAR studies (Fig.3) indicated that there is reasonable inverse correlation between molecular area and molecular volume and the activity against RT2 cells. We also found that lower values of HOMO energy contribute to higher cytotoxic activity against T98 cells. In addition, we suggest that the lowest hydrogen bonding ability of the compounds the highest their cytotoxic activity.

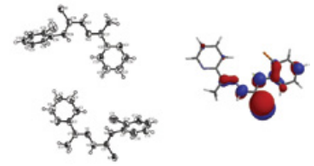

Figure. 3 HOMO density distributions of H2Ac4oClPh

The studied thiosemicarbazones can activate apoptotic pathways by mechanisms that are both dependent and independent of p53, and can probably recruit more than one pathway to trigger cell death. The high cytotoxic effect of the compounds against glioma cells at nanomolar doses suggests that they are promising as drug candidates.

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The Influence of b-Substituents in Aldol Reactions of Boron Enolates of b-alkoxy Methylketones

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doi:10.1021/ol102303p

The aldol reactions of boron enolates generated from β-alkoxy methylketones and achiral aldehydes frequently favors the formation of the 1,5-*anti* aldol adduct. Recently, Goodman and Paton proposed that the sense of the observed asymmetric induction proceed via boat-like transition states involving a formyl hydrogen bond with the b-oxygen that stabilizes the competitive transition states **IN-1,5-ANTI** leading to the 1,5-*anti* isomer, and the **IN-1,5-SYN** leading to the 1,5-*syn* isomer (Figure 1).[1] To small and medium P groups (like a PMB protecting group) the **IN-1,5-ANTI** transition state is lower in energy than **IN-1,5-SYN** transition state preventing the interactions between b-alkyl R group and the boron ligands (L). However, larger P groups (like TBS or *t*-Bu protecting group) lead to steric interactions between P and R groups balancing the energies of both transition states with low 1,5-*syn* selectivity being observed in same cases.[2]

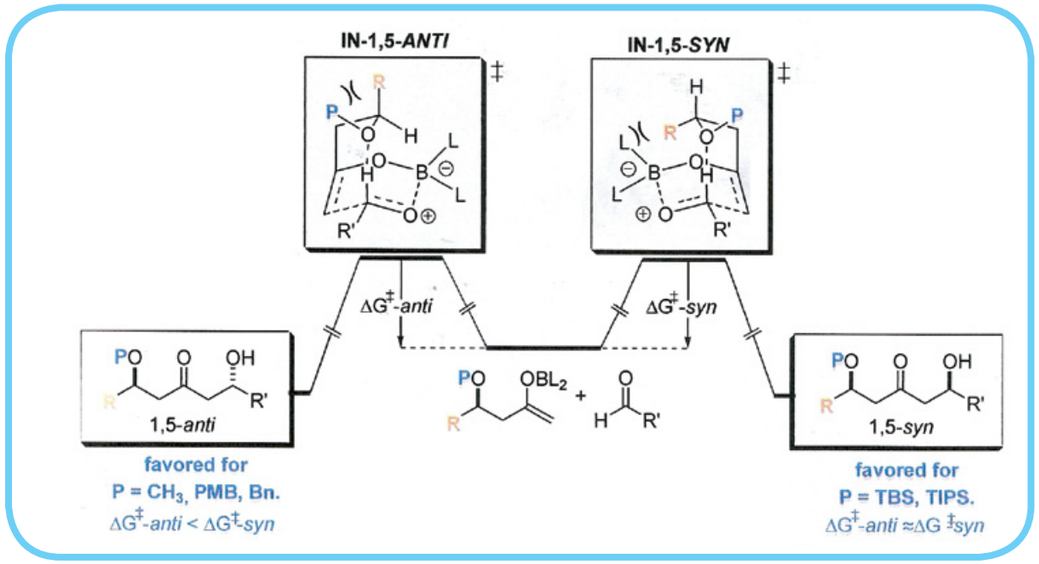
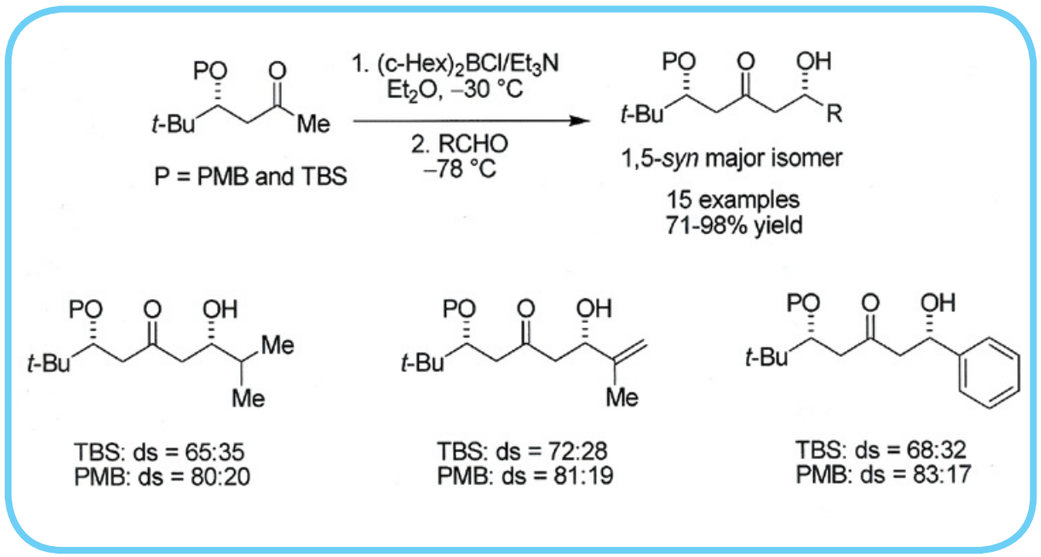


Figure 1: 1,5 Aldol reaction pathway for b-alkoxy methylketones and aldehydes.

In this paper we demonstrated that it is possible to obtain moderate levels of 1,5-*syn* induction from β-*t*-butyl-β-alkoxy methylketones independent of the nature of the β-alkoxy protecting group (P). The aldol reactions were found to proceed with good yields and good levels of remote 1,5 stereoinduction providing 1,5-*syn* isomers as the major products (Scheme 1).



Scheme 1: Aldol Reaction of b-Alkoxy Methylketones.

Notably, these reactions gave the 1,5-*syn* isomer, opposite to boron aldol reactions of simple β-alkoxy methylketones, indicating the contribution from the bulky substituent at the β-position showing that the volume of the substituent in β is crucial for the control of remote stereochemistry in aldol reactions involving boron enolates of methyl ketones. Thus, it is clear that the greatest contribution to the sense of 1,5-*syn* induction is related to the stereo effect of the substituent in β. In our previous work we also found a remarkable influence of the β−trichloromethyl bulky group (R = CCl3) on the stereochemical course of these aldol reactions leading to good levels of 1,5-*syn* induction, independent of the nature of the β−alkoxy protecting group (P = Bn and TBS).[3]

In order to clarify this, we have performed theoretical calculations using density functional theory (B3LYP) on the competing transition structures leading to both 1,5-*anti* and 1,5-*syn* aldol adducts. For R = CCl3 and *t*-Bu of the simple aldol transition structures for the dimethylboron enolates and acetaldehyde, the competitive boat-like transition states containing stabilizing hydrogen bonds are higher in energy when compared with the corresponding **OUT-1,5-*ANTI*** and **OUT-1,5-*SYN*** transition states, lacking the formyl H-bond (Figure 2). The analysis of the relative energies of these transition states shows relative energies favoring the corresponding **OUT-1,5-*SYN*** transition structure, thus preventing the steric interactions of bulky R groups and supporting the formation of the 1,5-*syn* diastereoisomer.

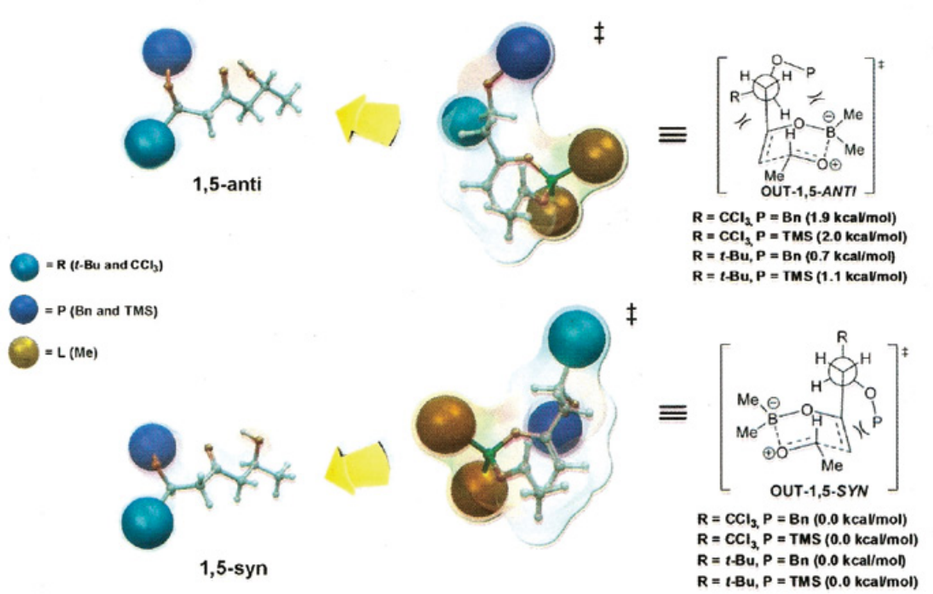


Figure 2: Relative energies for boat-like transition structures obtained using B3LYP/6-31G(d,p). Single-point energy (CPCM-uaks) in B3LYP/6-31+G(d,p).

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Microwave-assisted synthesis and structure–activity relationships of neuroactive pyrazolo[3,4-*b*]pyrrolo[3,4-*d*]pyridine derivatives

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doi:10.1016/j.bmcl.2009.11.038

Zolpidem is an imidazo[1,2-*a*]pyridine derivative commonly used to treat anxiety disorders, acting as benzodiazepine receptor agonist. The ability of zolpidem to relief the post-operative and low back pain is also been reported. In this context, we described previously the discovery of the new potent analgesic and sedative heterotricyclic derivative LASSBio-873, which was structurally designed as zolpidem analogue. Despite the important bioprofile displayed by LASSBio-873, it pre-clinical development was retarded by difficulties in the synthetic key-step used to construct this derivative, which had low yield (35%) and long reaction time (48 h). For this reason, this work describes the advantages of a solvent free reaction using microwave (MW) irradiation at the key cycloaddition step exploited to obtain LASSBio-873 (Figure 1), and the application of the developed methodology to prepare new heterotricyclic analogues and characterize its comparative sedative profile.

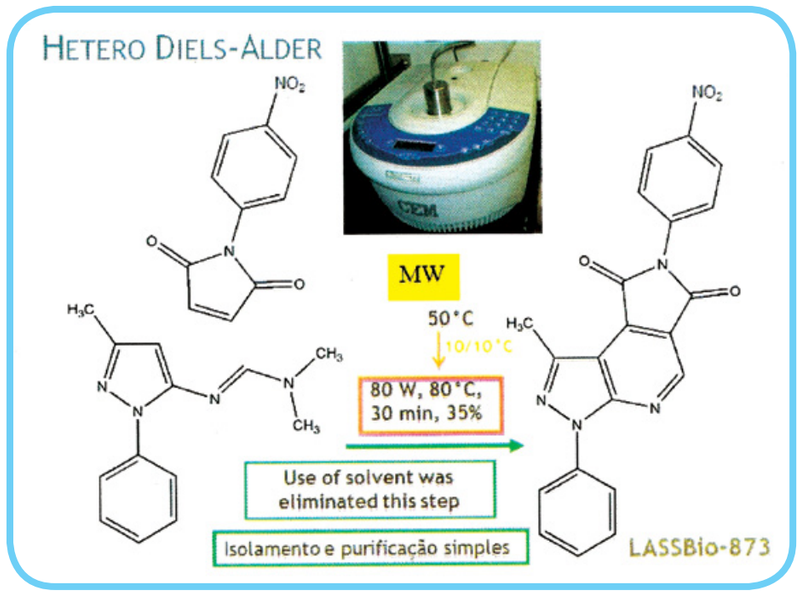


Figure 1. The cycloaddition step exploited to obtain LASSBio-873.

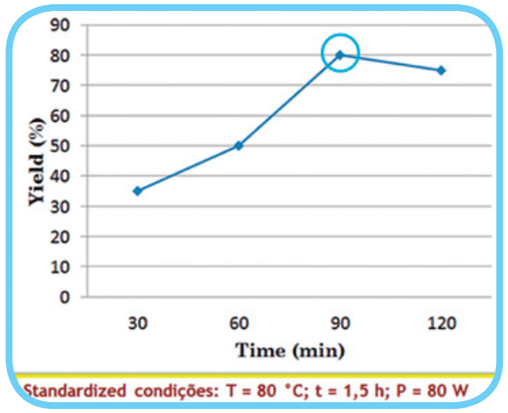
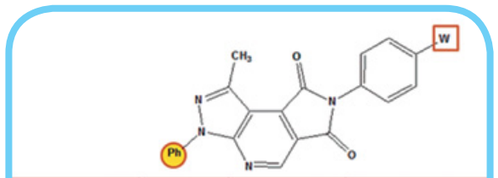


Figure 2. Optimization of the reaction time and yields during the preparation of LASSBio-873 under MW irradiation.



Compound	W	Yield (%) Δ, (50°C), 48 h	Yield (%) MW (80°C), 1.5 h
LASSBio-1424	OMe	----	35
LASSBio-980	Me	25	30
LASSBio-981	H	25	50
LASSBio-872	Cl	20	40
LASSBio-1457	CO_2H	----	30
LASSBio-873	NO_2	35	80

Figure 3. Synthesis of N-phenyl pyrazolo[3,4-*b*] pyrrolo[3,4-*d*]pyridine derivatives from series A exploiting hetero Diels–Alder reaction under MW irradiation in solvent-free conditions.

Adapting the methodology described before to construct the heterotricyclic ring of LASSBio-873 using conventional heating to a new procedure that use solvent free conditions to perform the hetero Diels-Alder cycloaddition of N-phenylpyrazole azadienes with *N*-phenylmaleimides under MW irradiation. After exhaustive investigation of the experimental conditions applied for this reaction we were able to obtain the sedative prototype faster and in better yields (Figure 2).

Using AcOH as solvent, this procedure lead to obtention of LASSBio-873 in 35% yield, after 48 h under conventional heating (Figure 3). On the other hand, exploiting solvent-free conditions and MW irradiation we were able to obtain target compound after 1.5 h, in 80% yield (Pmax=80W, T=80°C and open vessel) (Figures 1 and 2). When time, temperature and potency of the MW oven were altered, we detected the production of side compounds and the consequent reduction of LASSBio-873 yields (Figure 2).

The developed methodology was applied to prepare other heterotricyclic *N*-methyl analogues from series B (Figure 4), in order to perform structure sedative activity relationships.

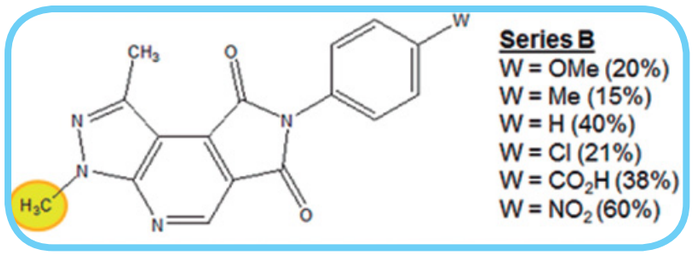


Figure 4. Structure and yields of *N*-methyl pyrazolo[3,4-*b*]pyrrolo[3,4-*d*]pyridine derivatives from series B, prepared from hetero Diels–Alder reaction under MW irradiation.

Excepting LASSBio-873 and LASSBio-1424, the sedative profile produced by heterotricyclic derivatives from series A and simplified *N*-methyl analogues from series B in the locomotor activity test in mice was extremely reduced by proposed structural changes. On the other hand, the highest sedative activity displayed *para*-nitro derivative (LASSBio-873) and the novel *para*-methoxy derivative (LASSBio-1424), both from series A, indicate that these two groups are potential pharmacophoric points, to be recognized as H-bond acceptors with complementary residues of occasional target bioreceptors. Moreover, absence of sedative activity in derivatives from series B (Figure 4) highlighted the possible influence of the phenyl group bonded to the pyrazole ring of the pyrazolo[3,4-*b*]pyrrolo[3,4-*d*]pyridine system to potentiate the sedative profile of these heterotricyclic derivatives.

As concluding remarks, beyond scale up facilities provided by the absence of solvent, time spent in the cycloaddition step exploited to prepare LASSBio-873 was drastically reduced. In addition, the desired bioactive compound could be obtained in higher yields, after a work-up of reaction mixture, through an eco-friendly approach. The developed new methodology facilitate the large scale production of LASSBio-873, enabling the preclinical studies to validate their profile as neuropathic pain modulator.

Design of New dopamine D2 receptor ligands: Biosynthesis and pharmacological evaluation of the hydroxylated metabolite of LASSBio-581

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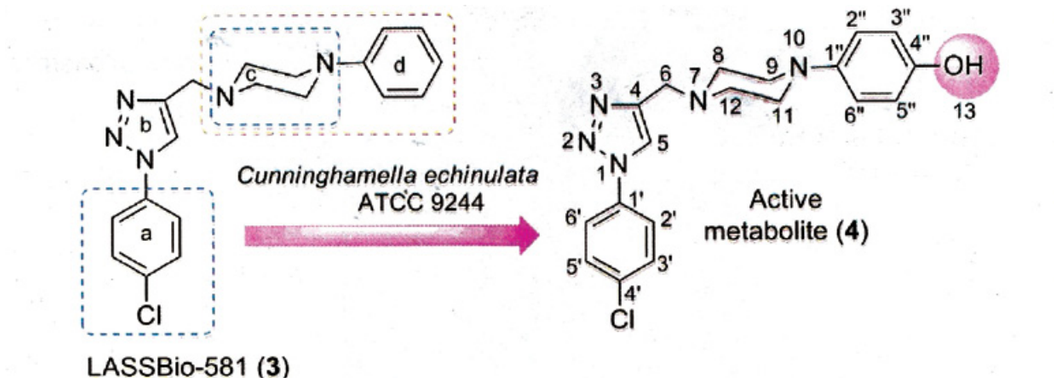
Bioorg. Med. Chem. Lett. (2010) 20: 2888-2891.
doi:10.1016/j.bmcl.2010.03.034

The *N*-phenylpiperazine derivative, LASSBio-581 (**3**), was designed as a selective ligand of dopamine D2 receptor with agonist activity modulated by chlorine atom in the aromatic ring and hypothermic action in assays with apomorphine in mice. The mechanism of action through the serotonergic neurotransmitter system was observed in subsequent evaluation. Pharmacokinetics studies of LASSBio-581 have been performed in rats.

This previous study showed that LASSBio-581 is absorbed by oral and intra-peritoneal routes of administration, showing a two-phase pharmacokinetic disposition, but metabolites weren't identified. The aim of the present work was to use filamentous fungi to biosynthesize large amounts of the *p*-hydroxylated metabolite of LASSBio-581 (**4**) and to perform pharmacological evaluation of **4**.



Cunninghamela chinulata ATCC 9244 produced the major quantity of metabolites, therefore, was selected for the preparative-scale biotransformation of LASSBio-581. After 72 h of incubation, LASSBio-581 disappeared of the surnageant and *Cunninghamella echinulata* ATCC 9244 produced basically the metabolite (**4**) at high concentrations in 24 h.

Compound **4** was obtained after recrystalization as white crystals, yield of 62.5 %, melting point 78.1 °C. The X-ray analysis of **4** confirms the structure ascribed on the basis of the others spectra.

The pharmacological activity of the *p*-hydroxylated metabolite (**4**) biosynthesized was assayed for binding to serotonin and dopamine receptors. Table 3 shows the binding assays as reported elsewhere.

As we can infer from Table 3, LASSBio-581 binds with a moderate affinity to D2-like, 5-HT1A and 5-HT2A receptors. On the other hand, its *p*-hydroxilated metabolite, **4**, presents higher Ki values than LASSBio-581 for all these receptors, maintaining a similar moderate affinity just for D2-like receptors. The affinity for the 5-HT1A receptors decreased 6.5 fold whereas for 5-HT2A, no estimation of Ki was possible since the largest concentration used (30 μM) inhibited only 49 % of [3H]-ketanserin binding. Therefore, **4** can be considered more selective for dopamine receptors than LASSBio-581. This information is useful to design new neuroactive selective dopamine inhibitors based on the chemical structure of **4**.

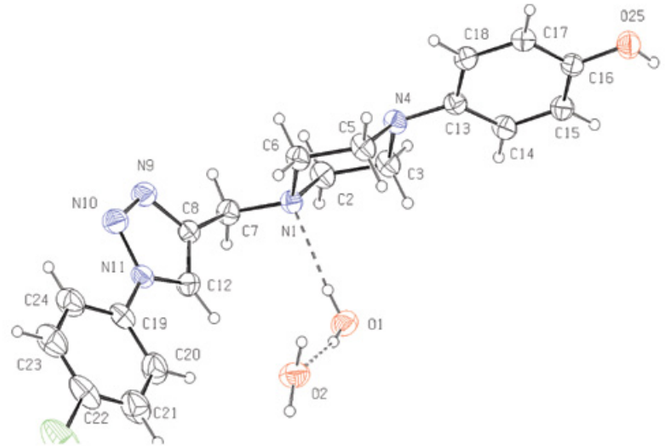
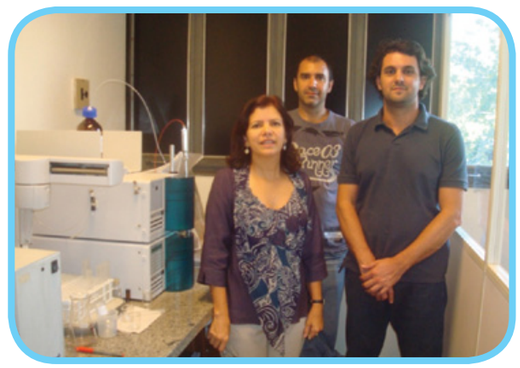


Table 3. LASSBio-581 and its metabolite (**4**) affinity for D2-like, 5-HT1A and 5-HT2A receptors.

Compound	Ki (μM)		
	D2-like	5-HT1A	5-HT2A
LASSBio-581	0.95	1.2	11
Metabolite (4)	1.7	8.0	>19[a]

[a] Binding inhibition of 49% at 30 μM.



Professors Oliveira, Menegatti and Sabino

Casearin X, Its Degradation Product and Other Clerodane Diterpenes from Leaves of *Casearia sylvestris:* Evaluation of Cytotoxicity against Normal and Tumor Human Cells

A. G.dos Santos, P. M. P. Ferreira, G. M.Vieira Jr, C. C. Perez, A. G. Tininis, G. H. Silva,V. da S. Bolzani, L.V. Costa-Lotufo, C. do Ó Pessoa, A. J. Cavalheiro

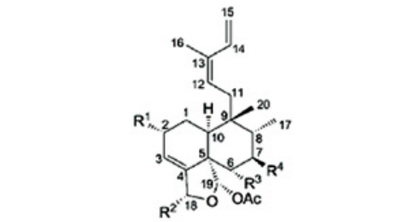
Chemistry & Biodiversity (2010) 7: 205-215
doi: 10.1002/cbdv.200800342

An EtOH extract of the leaves of *Casearia sylvestris* afforded new clerodane diterpene, casearin X, together with the known compounds casearins B, D, L, and O, and caseargrewiin F. Casearin X degraded to the corresponding dialdehyde when stored in $CDCl_3$. The diterpenes isolated were cytotoxic to human cancer cell lines, with caseargrewiin F being the most active and the new clerodane, casearin X, the second active compound with IC_{50} values comparable to the positive control doxorubicin. All isolated diterpenes showed lower activities against normal human cells than against cancer cell lines, which might indicate a possible selective action on cancer cells. Casearin X dialdehyde was not cytotoxic to cancer cells indicating that the occurrence of these CO groups at C(18) and C(19) is incompatible with the cytotoxic activity.

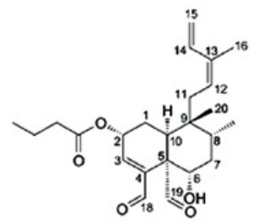
C. sylvestrys (Salicaceae) is a tree widely distributed in several ecosystems, and very known in Brazil due to its extensive uses in popular medicine for the treatment of snake bites, and also as anti-ulcer, anti-pyretic, and topical antiseptic.

Comp.	L-929	MOLT-4	Sel.	MDA/MB435	Sel.	HCT-435	Sel.	SF-295	Sel.
1	1.52	0.22	6.9	0.35	4.3	0.97	1.6	0.43	3.5
6	1.09	0.09	12.1	0.43	8.4	0.15	7.3	0.17	6.4
Dexoru-bicin	**1.20**	**0.05**	**24.0**	**0.83**	**1.4**	**0.02**	**60.0**	**0.40**	**3.0**

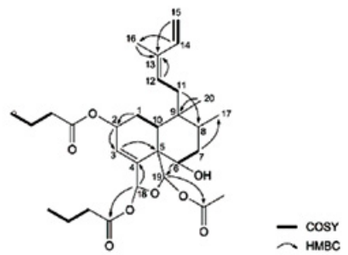
Table 1. Cytotoxic activity of clerodanes diterpenes from *C. sylvestris* in human cancer and normal cell lines, determined by MTT assay (IC_{50} [μM]).



	R^1	R^2	R^3	R^4
Casearin X (**1**)[1])	$PrCO_2$	$PrCO_2$	OH	H
Casearin B (**2**)[1])	MeO	AcO	AcO	$PrCO_2$
Casearin D (**3**)[1])	OH	$PrCO_2$	OH	$PrCO_2$
Casearin L (**4**)[1])	MeO	$PrCO_2$	AcO	OH
Casearin O (**5**)[1])	MeO	$PrCO_2$	AcO	$PrCO_2$
Caseargrewiin F (**6**)[1])	$PrCO_2$	AcO	OH	H



7[1])



Interleukin-33 attenuates sepsis by enhancing neutrophil influx to the site of infection

J. C. Alves-Filho, F. Sônego, F. O .Souto, A. Freitas, W. A Verri Jr, M. Auxiliadora-Martins, A. Basile-Filho, A. N McKenzie, D. Xu, F. Q. Cunha and F.Y. Liew

Nature Medicine (2010) 16: 708–712
doi:10.1038/nm.2156

Sepsis is a systemic inflammatory condition following bacterial infection with a high mortality rate and limited therapeutic options. IL-33 is a recently identified member of the IL-1 family that binds the heterodimeric receptor complex consisting of ST2 (IL-1RL1) and IL-1 receptor accessory protein. Here we show that interleukin-33 (IL-33) reduces mortality in mice with experimental sepsis from cecal ligation and puncture (CLP). IL-33–treated mice developed increased neutrophil influx into the peritoneal cavity and more efficient bacterial clearance than untreated mice (Figure 1).

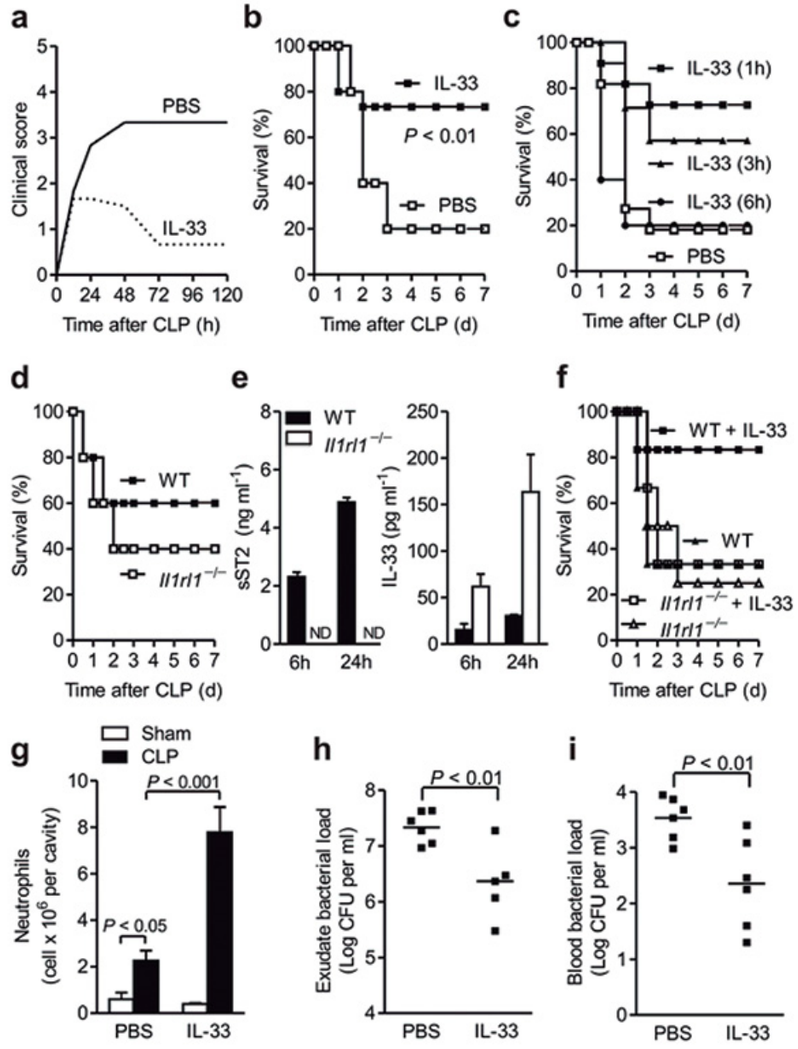


Figure 1. IL-33 attenuates sepsis and increases neutrophil influx to the site of infection and bacteria clearance. (a,b) Clinical signs (a) and mortality (b) after IL-33 (1 μg per mouse per injection) was injected i.v. 24 and 1 h before CLP on naive BALB/c mice. Data are pooled from three experiments, n = 6 mice per group per experiment. (c) Time course of IL-33 treatment. IL-33 (1 μg) was injected i.v. as a single dose 1, 3 or 6 h after CLP in BALB/c mice. (d) Survival rate of untreated Il1rl1−/− and WT mice given a milder form of CLP. (e) sST2 and IL-33 concentration in the peritoneal lavage fluid of WT and Il1rl1−/− CLP mice, as determined by ELISA. Similar results were obtained in the serum of the CLP mice (data not shown). (f) Survival rate of Il1rl1−/− and WT CLP mice treated with IL-33 as in a. (g) Number of neutrophils in the peritoneum of CLP or sham-operated mice treated with IL-33 or PBS. (h,i) Bacterial loads in the peritoneum (h) and in the blood (i) of CLP mice treated with IL-33 or PBS. Data are means ± s.e.m., n = 5–10 mice per group and are representative of three experiments (h,i). *P < 0.05.

Activation of Toll-like receptors (TLRs) in neutrophils downregulates CXCR2 expression and impairs neutrophil migration. We show here that IL-33 prevents the downregulation of CXCR2 and inhibition of chemotaxis induced by the activation of TLR4 in mouse and human neutrophils. Furthermore, we show that IL-33 reverses the TLR4-induced reduction of CXCR2 expression in neutrophils via the inhibition of expression of G protein–coupled receptor kinase-2 (GRK2), a serine-threonine protein kinase that induces internalization of chemokine receptors (Figure 2). Together, our results indicate a previously undescribed mechanism of action of IL-33 and suggest a therapeutic potential of IL-33 in sepsis.

Professor Cunha team, Faculty of Medicine, Universidade de São Paulo, Ribeirão Preto, S.P., Brazil.

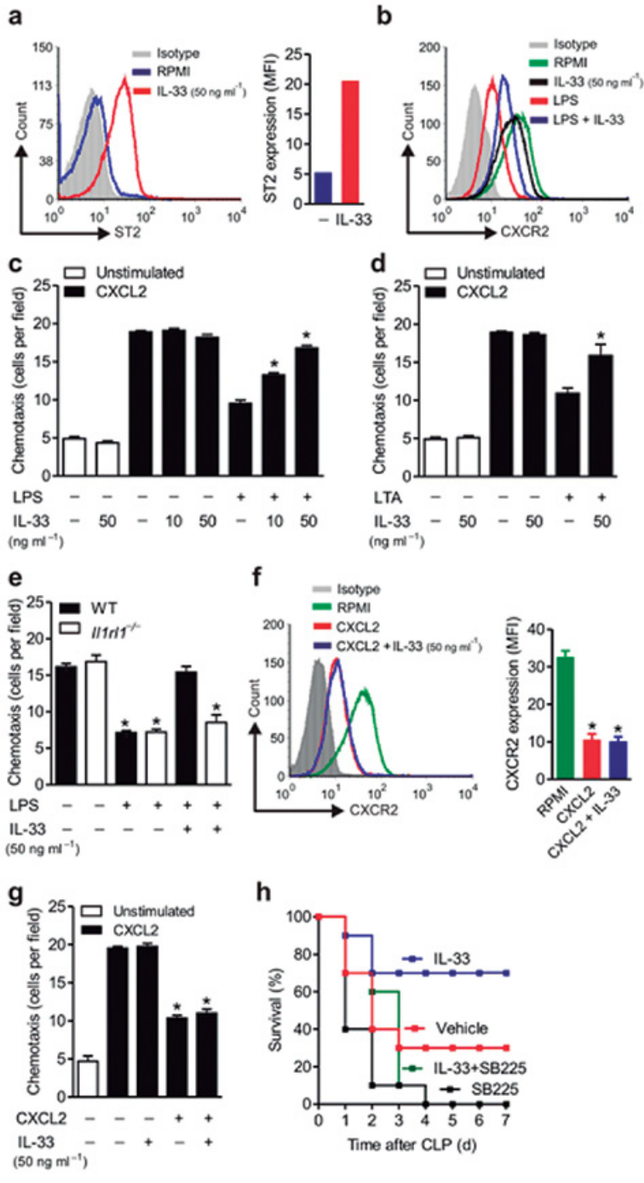


Figure 2: IL-33 blocks the downregulation of CXCR2 and chemotaxis mediated by LPS in vitro. (a) FACS analysis of naive BALB/c bone marrow neutrophils cultured with IL-33 or medium (RPMI) overnight and stained for ST2. (b–g) Neutrophils were purified from the bone marrow of naive mice and cultured for 1 h with LPS (1 μg ml−1), LTA (1 μg ml−1), IL-33 (10–50 ng ml−1), CXCL2 (30 ng ml−1) or a combination of these reagents, as indicated. The expression of CXCR2 (b,f) and chemotaxis to CXCL2 (c,d,e,g) were determined. In some experiments (g), neutrophils were pretreated with CXCL2 or IL-33 before assaying for chemotaxis toward CXCL2. Data are means ± s.e.m., n = 5 replicates per group. *P < 0.05 versus cultures without IL-33 (c,d), untreated neutrophils (e), or cells not pretreated with CXCL2 (g). (h) Survival of CLP mice treated with IL-33 with or without the CXCR2 inhibitor SB225002 (10 mg per kg body weight). Data are representative of two experiments, n = 10 mice per group.

INCT-INOFAR
INITIATIVES FOR
THE PROMOTION
OF SCIENTIFIC
AWARENESS AND
POPULARIZATION
OF SCIENCE

INCT-INOFAR
Annual Activities Report
2010

75

Scientific Awareness and Popularization of Science

With a goal of increasing critical consciousness in the general population about the correct use of medications, publicizing basic scientific knowledge in the area of Pharmaceutical Sciences, **INCT-INOFAR** dedicates itself to scientific awareness and health education initiatives.

"Nowadays, it is not enough to just write papers and register patent requests, it is necessary to develop tools to spread knowledge to society, and as such, promote social inclusion through Science"

Professor Eliezer J. Barreiro, **INCT-INOFAR** Coordinator.

INCT-INOFAR believes that the popularization and increased awareness in the fields of Science, Technology, and Innovation are a very important factor in enabling the population to be critically aware of the current globalized world, also allowing that young people may find themselves draw to new vocations, even if those are unrelated to their family history.

Two educational booklets, five different versions of theme puzzles, as well as a video make up the scientific awareness and health education materials that have been produced by **INCT-INOFAR**.

At 13 minutes long, the scientific publicizing video "LASSBio 596: from molecule to medication" (www.inct-inofar.ccs.ufrj.br/videos.html) describes the path of a new substance developed by **INCT-INOFAR** to fight asthma, presenting all the necessary research stages so that the medication can reach the shelves of drugstores.

The educational booklets and the theme games attempt to make the public more aware of the correct usage of medications. The idea is that through reading cartoons and assembling puzzles, they can be encourage to reflect on the subject, which would lead to increased awareness in individuals when faced with the use of medications.

Among the themes approached in the scientific awareness materials are the influence of advertisement done by the pharmaceutical industry, the attention to the purchase of bootleg medications, the risks in self-medicating, information on the different prescription categories in medications, and tips to safely store medications at home. Promoting awareness in future public health campaigns is also something **INCT-INOFAR** is interested in.

Pharmaceuticals Portal

www.portaldosfarmacos.ccs.ufrj.br

The **Pharmaceuticals Portal** is the web tool that **INCT-INOFAR** uses to publicize and popularize Pharmaceutical Sciences. Through this portal, **INCT-INOFAR** publicizes its research activities in layperson's language, and makes its health education materials available.

In sync with new trends in scientific journalism, the **Pharmaceuticals Portal** provides the calendar and coverage of relevant scientific events in the area, publishing original reports on current themes in the areas of innovation in pharmaceuticals and medications, as well as health in general.

The importance of vaccination for adults, the difficulty in producing a 100% national generic medication, the rational use of medications in teenagers, patient safety, patents and pharmaceutical innovation, animal testing, pharmaceuticals from ocean materials, malignant hyperthermia, and advances in medicinal chemistry were a few of the themes highlighted in articles on the **Pharmaceuticals Portal** in 2010.

In May, the **Pharmaceuticals Portal** published the story "Science closer to winning the fight against generalized infection" when an article* by the research group led by Professor Fernando de Queiroz Cunha (USP-Ribeirao Preto), **INCT-INOFAR** associate researcher, was published in *Nature Medicine* journal, a periodical with significant (27,5) impact on the international scientific community. .

"A discovery that might be a new path in the development of new therapies for fighting generalized infection (sepsis) has garnered Brazilian researchers a publication in Nature Medicine, one of the most renowned journals in the field. The result of cooperation research between the Laboratory of Inflammation and Pain of the Department of Pharmacology of the Faculty of Medicine at USP Ribeirao Preto and the Biomedical Research Center of the University of Glasgow in the United Kingdom was published last Sunday, May 16, on the online version of the science journal.

Considered to be one of the main causes for admission to Intensive Care Units (ICUs), the number of deaths from sepsis in Brazil is higher than those from cancer and myocardial infarctions. In spite of the advances in medicine and of high investments from the pharmaceutical industry, the incidence and the mortality rates of the illness have not diminished worldwide. The USP-Ribeirao Preto researchers have been studying the biochemical mechanisms responsible for the inflammatory response for a few years, and they were pioneers in showing that, during sepsis, there is a failure of neutrophils to migrate to the infectious focus, which intensifies the gravity of the illness.

In this new study, in partnership with the British researchers, the Brazilian scientists discovered that cytokine IL-33 is capable of diminishing sepsis by reestablishing the migration of neutrophils to the infectious focus, therefore fighting the development of generalized inflammatory processes. By elucidating the role of this cytokine in the physiopathology of this illness, science takes a step towards finding new therapeutic approaches to heal sepsis. Currently, antibiotics are the pharmaceuticals most used in ICUs to try to control generalized infection; however, in many cases they are inefficient due to bacterial resistance to the medication. (...)"

Source: **Pharmaceuticals Portal**
Interleukin-33 attenuates sepsis by enhancing neutrophil influx to the site of infection

With the perspective of popularizing Science, the **Pharmaceuticals Portal** has created a specific section in the website to encourage future scientists to create their own methodologies to take the knowledge they have acquired in a University to society. At this section, young researchers write reviews of important discoveries recently published in pharmaceuticals and medications journals. They also act as scientific journalists, by conducting question and answer interviews with the authors of these papers.

The **Pharmaceuticals Portal** publishes cartoons every month with a critical message on the irrational use of medications, suggesting conscious alternatives for their usage. The danger of consuming alcohol when using medications, the three commandments of the safe and correct usage of medications, and the drugstore as the only authorized reseller or medications have been themes for cartoons in the past. From the cartoon library in the **Pharmaceuticals Portal**, INCT-**INOFAR** selected 5 to be used in their theme puzzles.

Away from the web world, **INCT-INOFAR** was able to promote its scientific popularization and health education activities in the XX Pan American Pharmacy Congress, which took place in Porto Alegre – RS, being held in Brazil for the first time ever, on May 2010. At the occasion, the event participants were able to see the educational materials developed by **INCT-INOFAR** up close, including the materials created to teach children about the correct use of medications.

I Scientific Awareness Theme School

As far as activities to increase scientific awareness and publicize Science go, **INCT-INOFAR** joined four other National Institutes of Science and Technology (INCT of Functional Complex Materials, INCT for the Biorational Control of Pests and Insects, INCT for Immunology Research and the INCT for Energy and Environment) to organize, on October 14, 15, and 16, the I Scientific Awareness Theme School. The event was an initiative of the I5+ group , a group initially formed by 5 INCTs that came together, on late 2009, to discuss governance issues and to establish scientific and technological cooperation bonds.

www.inct-inofar.ccs.ufrj.br/i5.html

On the occasion, the representatives of each INCT present had the opportunity to present, in detail, their scientific awareness projects, promoting the exchange of ideas and methodologies in an area that represents a new field to be explored by scientists.

"Currently, in the INCTs, scientific awareness is no longer an afterthought, but part of the fundamental goals. Maybe this is the great new thing in Science in Brazil: high quality researchers paying attention to a topic that was placed aside in the past", highlighted Professor Angelo da Cunha Pinto (UFRJ), a member of the Governance and Follow-Up Committee (CGA) of **INCT- INOFAR**.

Taking advantage of the common thread of Chemistry that runs through all 5 of the INCTs, the I Scientific Awareness Theme School had a lecture by the researcher responsible for the activities that will celebrate, in 2011, the International Chemistry Year in Brazil.

For most participants, the I Scientific Awareness Theme School was a positive experience. Presentations showed that the National Institutes are all committed to developing scientific awareness and popularization activities.

"If they come together and properly connect, the costs and time invested may be optimized, and the programs that each Institute are conducting individually might be improved and advanced", said Professor Jailson Bittencourt, INCT of Energy and Environment (E & A) Coordinator, one of the founding members of I5+

"The Correct Use of Antibiotics" Booklet

In November 2010, **INCT-INOFAR** edited and produced a booklet called: "Joey's Friends in: The correct use of antibiotics". In cartoon format, the educational material warns of the risks in the improper use of medications, showing common everyday practices that lead to increasing bacterial resistance.

Through the story of Joey's illness, the booklet explains in easy to understand to laypeople scientific language why and how certain bacteria can become resistant to antibiotics. It also calls attention to the importance of consulting a doctor, and especially of following what was prescribed strictly.

The booklet was produced by **INCT-INOFAR** under the supervision of the National Health Surveillance Agency (Anvisa), who made the material available on its website a week after publishing the new rules and regulations for the sale of antibiotics in drugstores (RDC 44 – October 26, 2010). This is the second educational material published by **INCT-INOFAR** aimed at increasing awareness in the correct use of medications.

INCT-INOFAR in the Electronic Journal of Chemistry

The Electronic Journal of Chemistry (RVq) released, in September 2010, a special issue fully focused on **INCT-INOFAR** research. The six articles in the publication are fully dedicated to radical innovation, presenting some of the most relevant results achieved in 2010 by the research groups that make up the Institute.

The articles report on the results of studies that range from the molecular planning and identification of authentic candidates for new anti-inflammatory, analgesic, and anti-asthmatic medications – acting through original pharmacological mechanisms – to the discovery of new structural patterns of synthetic origin with properties on the Central Nervous System and as chemotherapeutic agents.

The Electronic Journal of Chemistry (RVq) is an initiative of Regional Secretary of the Brazilian Society of Chemistry in Rio de Janeiro (SBQ-Rio). It is an electronic journal published quarterly (www.uff.br/rqv) and freely accessible online, created to be used as a reference source and for publicizing articles in Portuguese about Chemistry and related areas. On request of the Electronic Journal of Chemistry team, Lidia Moreira Lima, Scientific Supervisor of **INCT-INOFAR**, was responsible for this special issue of the RVq dedicated to the Institute.

Illustrating different approaches used in the design/ Discovery of new bioactive prototypes, this theme issue of the Electronic Journal of Chemistry proves the scientific expertise available in Brazil in the area of Medicinal Chemistry. It also shows how bringing together research teams made up of experts in different knowledge areas allows for multi and interdisciplinary characteristics to work for the improvement of the chain of technological innovation in pharmaceuticals and medications in Brazil.

Summary of articles published in RVq – INCT-INOFAR special edition

"*Benzaldeído semicarbazona: um candidato a fármaco que alia simplicidade estrutural a um amplo perfil de atividades*" ("Benzaldehyde semicarbazone: a pharmaceutical candidate which combines structural simplicity to a wide range of activity")

This work describes the studies with benzaldehyde semicarbazone (BS) in the search for analgesic, anti-inflammatory, and anticonvulsant medications.

"*LASSBio-596: da descoberta aos ensaios pré-clínicos*" ("LASSBio-596: from discovery to pre-clinical assays")

This article reviews the trajectory of discovery of a new candidate for anti-asthma pharmaceutical to the first pre-clinical assays, with a focus on a murine model of chronic and acute asthma.

"Descoberta de novos protótipos N-fenilpiperazínicos heteroarilazólicos candidatos a fármacos antipsicóticos atípicos" ("Discovery of new N-fenilpyperazine heteroarilazolic candidates to atypical antipsychotics")

This work describes the discovery of new neuroactive prototypes, planned from the structural simplifying of the atypical antipsychotic pharmaceutical clozapine, which resulted in compounds with a probable indication for the treatment of schizophrenia.

"Espectalina, cassina e análogos semissintéticos como potenciais candidatos a fármacos para o tratamento da doença de Alzheimer" ("Spectaline, cassin, and semisynthetic analogs as potential candidates to pharmaceuticals for the treatment of Alzheimer's disease")

This article describes the results of studies on the structural modifications of the piperidine isolate alkaloid of *Cassia sp*., which produced new structural patterns of selective inhibitors of acetyl-cholinesterase, candidates to agents indicated for the treatment of Alzheimer's disease.

"A Contribuição dos Produtos Naturais como Fonte de Novos Fármacos Anticâncer: Estudos no Laboratório Nacional de Oncologia Experimental da Federal University of Ceará" ("The Contribution of Natural Products as Sources of New Anticancer Pharmaceuticals: Studies in the National Laboratory of Experimental Oncology of the Federal University of Ceara")

This work narrates the recent efforts in the determining of *in vitro* and *in vivo* antitumoral activity of compounds obtained in the Caatinga, Atlantic Forest, Amazon, Cerrado, and Marine Ecosystems.

"*Proteínas tirosinas quinases: Desafios do desenvolvimento de fármacos para a terapia do câncer*" ("Tyrosine kinase proteins: Challenges of the development of pharmaceuticals for cancer therapy")

This article revisits the impact of the discovery of tyrosine kinase proteins (PTKs) in cancer therapy (such as imatinib) and discusses the challenges faced in rational planning of new PTK inhibitors.

INCT-INOFAR in the Media

In December 2010, an incremental innovation by **INCT-INOFAR** had great repercussion in the Brazilian and foreign press. In the same month in which the patent for Lipitor ®/ Pfizer expired in Brazil, **INCT-INOFAR** researchers announced the discovery of a new synthesis route for the production of its active principle, atorvastatin.

With a more efficient synthesis process, the novel route developed by **INCT-INOFAR** received media attention due to the high market impact of such a discovery. As a constant usage medication to reduce cholesterol that is widely adopted, Lipitor® is the best-selling drug worldwide. It is estimated that its sales in Brazil in 2009 alone have generated 400 million Reais to the patent holder.

The Brazilian science community was informed first hand, after a note was published on the Science Journal (*Jornal da Ciencia* – JC) on December 8, 2010. A week later, O Globo newspaper published a report on it on its science section, which made the press in general aware of the discovery of the novel synthesis of atorvastatin. This news was republished in the websites of different Ministries, like Health, Planning, Foreign Affairs, Development, Industry, and Foreign Trade, among others.

portal.saude.gov.br/clipping
www.itamaraty.gov.br/colesterol
www.inpi.gov.br/imprensa

Following that, the **INCT-INOFAR** achievement was publicized all over Brazil due to the great reprint potential of Agencia Estado news agency in online, print, and radio media. "Process may make cholesterol medication cheaper" was how the discovery was mentioned in the websites of publications like Estadao, Veja, Isto é, G1, and then reprinted on several blogs and social network sites.

Radios and TVs also publicized the important discovery. TV crews from several networks took turns recording in the laboratory where the new route was discovered, among them TV Cultura and SBT. But only after the novel synthesis of atorvastatin was reported by Thomson Reuters did it reach international proportions. As well as being publicized in the USA and Europe, the news was made available in Asia. NTD TV, a Chinese network, reported on the **INCT-INOFAR** discovery on one of their news shows.

Even on the free online encyclopedia Wikipedia we can currently find mention of the discovery of a new more efficient synthesis route to produce atorvastatin by Brazilian researchers.

wikipedia.org

Clipping

Notícias INCTs/CNPq
8/12/2010
New synthesis route for atorvastatin, the main statin

Jornal da Ciência
8/12/2010
New production process for cholesterol medication discovered

Boletim Faperj
December 9 to 15, 2010
Drugs and Medicines INCT synthesizes cholesterol reducing drug

Jornal O Globo
14/12/ 2010
Brazil produces a better anticholesterol drug

Portal Unicamp
14/12/2010
Unicamp discovers new route to produce the world's most sold medication

Radio CBN Campinas
14/12/2010
Unicamp Chemistry Institute produces active principle in the most sold medication for cholesterol control

Estadão (Agência Estado)
14/12/2010
Process may reduce prices of cholesterol medication

Veja (Agência Estado)
14/12/2010
Unicamp: process may reduce prices of cholesterol medication

Sala de Imprensa CNPq
15/12/ 2010
New synthesis route for atorvastatin, the main statin

TVB Notícias (SBT Campinas e Litoral)
17/12/ 2010
World's most sold medication will have new generic version

Radio CBN
17/12/ 2010
Presenter: Andrea Ferreira

SBT Brasil (SBT Nacional)
17/12/ 2010
Researchers create cheaper cholesterol drug

Boletim Faperj
December 16 to 22, 2010
Researchers create alternative route for high cholesterol medication

Jornal da Cultura (TV Cultura)
20/12/ 2010
Brazilian scientists isolate active principle of medication

Radio Jovem Pan
20/12/ 2010
Brazil might have a new cholesterol medication

Reuters
29/12/ 2010
Brazil develops low-cost Lipitor

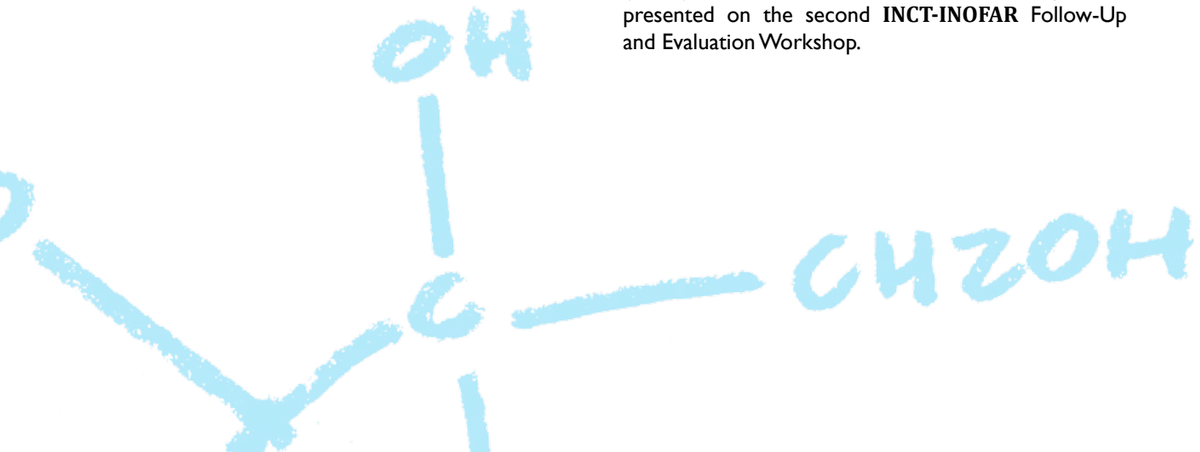
Jornal Correio Popular
31/12/2010
Medications at reduced prices

Events

Events promoted by INCT-INOFAR

The National Institute of Science and Technology of Drugs and Medicines (**INCT-INOFAR**) periodically organizes events with the goals of strengthening cooperation between its research groups, encouraging integration with National Institutes of Science and Technology (INCTs) of related areas, as well as attempting to establish partnerships with companies, NGOs, and other Institutions.

INCT-INOFAR researchers regularly attend events, lecturing and teaching workshops, being part of round tables and science fairs, thus actively contributing to knowledge being spread in the academic-scientific community. The Institute also supports courses and conferences, cooperating actively in the qualification of personnel and the advancement of new medication research in Brazil.

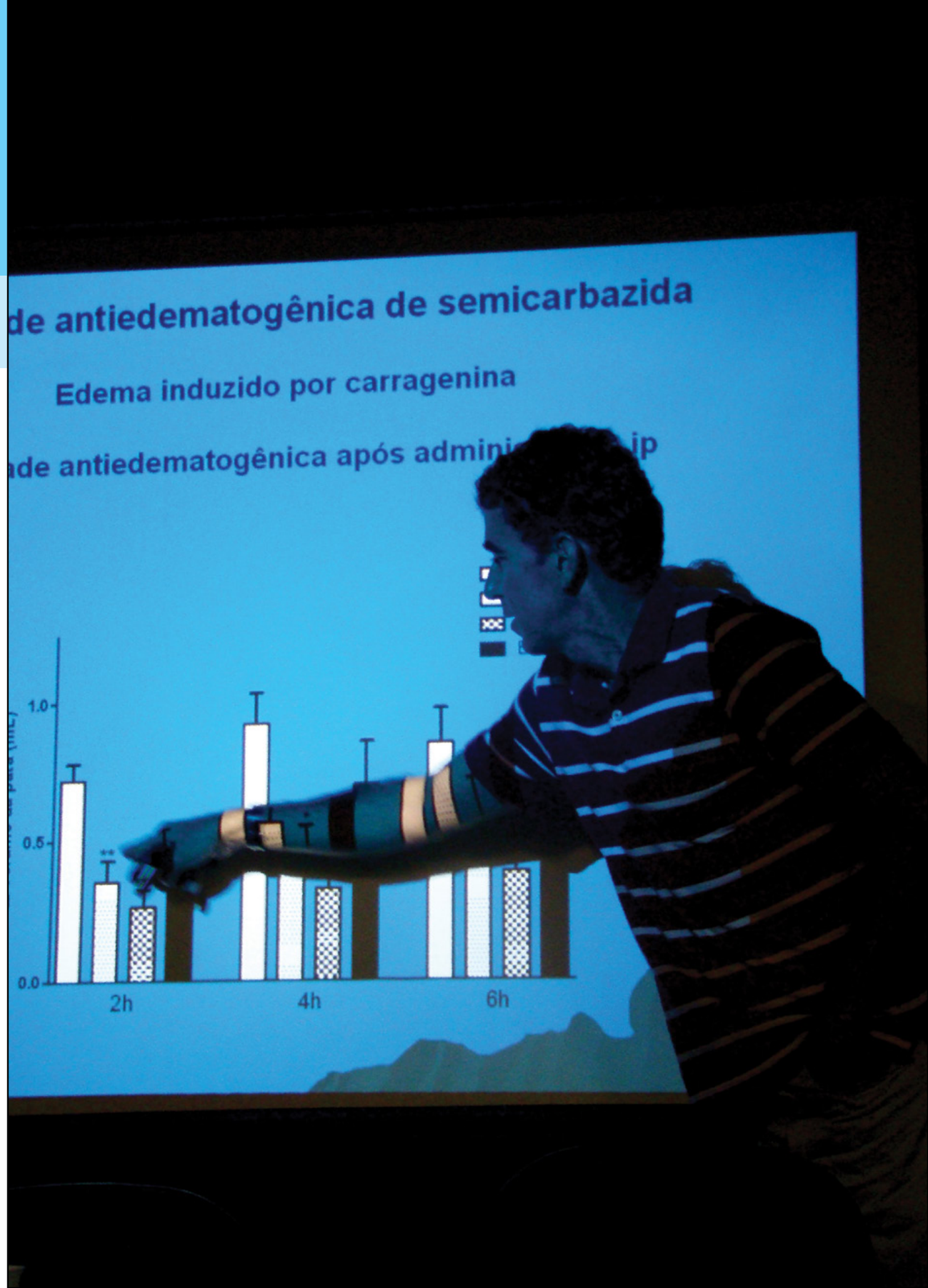


INCT-INOFAR Follow-Up and Evaluation Workshops

With a goal of presenting and discussing in person the results of its research projects, **INCT-INOFAR** organized Follow-Up and Evaluation Workshops with the presence of world renowned researchers who acted as consultants for the Institute. In 2010, **INCT-INOFAR** promoted two workshops at the Health Sciences Center of UFRJ, where the Institute is headquartered.

On March 10 and 11, the first Follow-Up and Evaluation Workshop of 2010 took place. In this event, incremental innovation projects in the field of generic medications were presented, as well the most advanced radical innovation projects. A month later, on April 19, researchers met again to discuss the results of intermediate stage projects in the **INCT-INOFAR** portfolio.

Chemistry expert Professor Dr. Vitor Francisco Ferreira from UFF was the external consultant for the first event. Pharmacologist Professor Dr. Joao Batista Calixto from the Federal University of Santa Catarina (UFSC) was the scientific consultant for the projects presented on the second **INCT-INOFAR** Follow-Up and Evaluation Workshop.



INCTs Follow-Up and Evaluation Meeting

On November 23 and 24 2010, the 1st Evaluation and Follow-up Meeting of the National Institutes of Science and Technology (INCTs) took place in Brasilia. The purpose of the event was to take stock of actions developed by the 122 INCTs since their creation, in the end of 2008. **INCT-INOFAR** representatives were at the event, which had around 500 participants among researchers, support agency managers, and members of INCT promoting institutions.

Subdivided into theme groups, simultaneously, the representatives of each of the Institutes presented partial results of their research and answered questions from an evaluation committee comprised of Brazilian and foreign experts. During the 40m allotted to **INCT-INOFAR**, Prof. Eliezer J. Barreiro (UFRJ), Project Coordinator, talked about the main research projects conducted by the Institute, highlighting the molecules further along in the chain of innovation.

Aware of the issues in his research area, the researcher called attention to the lack of laboratories working in primary scaling of substances, without which all stages of the current regulatory benchmarks cannot be met. "It is no use having brilliant papers written if we cannot transfer this knowledge to society", highlighted the **INCT-INOFAR** coordinator.

Parallel to the presentations, in the exposition area of the Parlamundi Convention Center, there was the INCTs show. As they walked through the booths, the audience present could know more about the workings of each Institute, and their scientific awareness activities.

www.inct-inofar.ccs.ufrj.br/download/aar/2009.pdf

www.inct-inofar.ccs.ufrj.br/videos.html

On this occasion, **INCT-INOFAR** officially released its *Annual Activities Report* 2009 and presented its projects in health education, like the booklets on the correct use of medications, theme puzzles, as well as the scientific awareness video "LASSBio 596: from molecule to medication".

Exhibits in Expos

FAPERJ 30 Years Expo

In March 2010, **INCT-INOFAR** was part of the FAPERJ 30 Years Expo, which took place in the Museum of Modern Art (MAM) of Rio de Janeiro. At the event celebrating three decades of the Foundation for Research Support in the State of Rio de Janeiro (FAPERJ), the institute had the opportunity to present in the booth named "Molecular Structures, Diseases, and Pharmaceuticals" its health education and scientific awareness projects.

At the occasion, **INCT-INOFAR** shared the booth with three other INCTs: Structural Biology and Bioimaging (INBEB), Molecular Entomology (INCT-EM) and Investigation in Immunology (INCT-iii), and it was able to show its scientific awareness video at a showing at the Museum's movie theater.

2nd Expo-Farmed

With a goal to publicize the projects in its research network, and to establish partnership liaisons with the business sector, on August 2010 **INCT–INOFAR** was part of the 2nd EXPO-FARMED, a business expo connected to the 4th *ENIFarMed – National Meeting for Innovation in Pharmaceuticals and Medications*. The event which took place in the city of Sao Paulo, in the Reboucas Convention Center is a consolidated forum to promote interaction of R D & I professionals of companies in the productive chain with the Science and Technology Institutes and Universities.

Support to events

XVII Summer School in Medicinal Pharmaceutical Chemistry

Traditionally organized by the Laboratory for Evaluation and Synthesis of Bioactive Substances (LASSBio), the Summer School in Medicinal Pharmaceutical Chemistry was incorporated to **INCT-INOFAR** as an extension and continuous education activity for undergraduate as well as graduate students.

The event, which always takes place at the Health Sciences Center of UFRJ during summer break, offers 5 days in a row of courses and conferences with renowned national and foreign experts in the area of Medicinal Pharmaceutical Chemistry.

Since its creation in 1995, the School has over 2,000 participants, and has received noted scientists responsible for developing innovative medications, like Simon Campbell (sildenafil) and Robin Ganellin (cimetidine), who could retell the history of their discoveries in person.

On this sixteenth edition of the event, a team of Latin American experts in the planning and evaluation of new pharmaceuticals for treatment of Neglected Tropical Diseases was present, as well as a German researcher who works in designing new pharmaceuticals that act on the Central Nervous System.

Prof. Hugo Cerecetto, *Universidad de la República (Uruguay)*
Prof. Mercedes Gonzales, *Universidad de la República (Uruguay)*
Prof Antonieta Rojas de Arias, *Fundación Moises Bertoni (Argentina)*
Prof. Stefan Laufer, *University of Tuebingen (Germany)*

Introduction to Medicinal Pharmaceutical Chemistry, Pharmaceuticals Metabolism and Toxicology, Introduction to Patents and Pharmaceutical Innovation, Computational Chemistry and Molecular Modeling were some of the courses taught at the XVI Summer School in Medicinal Pharmaceutical Chemistry.

Course "Relative aspects in the patent examination process in pharmaceuticals"

Aiming to qualify researchers associated to **INCT-INOFAR** in the area of patent requests in Pharmaceuticals, the Institute invited an expert from the National Institute of Intellectual Property (INPI) to give a crash course on the subject. On December 10, 2010, at the Library Auditorium in the Health Sciences Center, the course presented by Dr. Alexandre Lopes Lourenço (INPI) was attended by around 30 **INCT-INOFAR** researchers from all over the country.

Malignant Hyperthermia 200 Symposium

Malignant Hyperthermia is a rare genetic disease caused by the action of medications used during general anesthesia. Sadly, the pharmaceutical industry does not have a cure for this disease; there is only one hard-to-administer medication, sodium dantrolene, to revert the hypermetabolic syndrome caused by the adverse reaction to general anesthesia.

To reduce the mortality rates for Malignant Hyperthermia, it is important to have early diagnosis of susceptibility to the illness. Since 1993, this work has been carried out in the Malignant Hyperthermia Diagnostic Center of UFRJ, coordinated by Prof. Roberto Takashi Sudo, **INCT-INOFAR** associate researcher.

To celebrate the Center's science efforts with two hundred biopsies done on the skeletal muscle of people who have a personal or family history of the disorder, **INCT-INOFAR** supported the Malignant Hyperthermia 200 Symposium on October 1st, 2010, at the Health Sciences Center at UFRJ.

The event brought together researchers from the basic and clinical area, as well as pharmaceutical industry representatives and members of society. It also had the presence of the first patient submitted to a biopsy, and of her sister, who survived Malignant Hyperthermia in 1991.

At the Symposium, Professor Carlos Alberto Manssour Fraga of the Laboratory of Evaluation and Synthesis of Bioactive Substances (LASSBio/UFRJ) presented a few **INCT-INOFAR** ideas to plan new dantrolene analogs. Through molecular changing tools, it was possible to achieve new prototypes that are currently being evaluated for their skeletal muscle relaxing potential.

Events where INCT-INOFAR was present

December 08, 2010
National Institute for Intellectual Property – Rio de Janeiro
Lecture: "The interaction between Universities and Companies in the Brazilian Pharmaceutical Sector: Can it Happen?"
Prof. Eliezer J. Barreiro

December 02, 2010
XII Annual Science Meeting of the Butantan Institute – Sao Paulo
Lecture: "**INCT-INOFAR** and pharmaceutical technological innovation"
Prof. Eliezer J. Barreiro

November 11 to 13, 2010
XVIII Chemistry Meeting of the Southern Region
Estacao Embratel Convention Center – Curitiba
Theme Session: "Innovation and Development of Pharmaceuticals and Medications"
Prof. Eliezer J. Barreiro

November 19, 2010
Graduate School in Chemistry Seminar
Federal University of Santa Catarina
Lecture: "Horizons and Frontiers of Interdisciplinarity in Medicinal Chemistry"
Prof. Eliezer J. Barreiro

November 19, 2010
Discussions of the Research and Development in Pharmaceuticals Program
Federal University of Rio de Janeiro

November 23 and 24, 2010
INCTs Evaluation Meeting
Brasilia - DF
Prof. Eliezer J. Barreiro
Prof. Fernando de Queiroz Cunha
Prof. Angelo da Cunha Pinto
Prof. Lidia Moreira Lima

November 08, 2010
V Brazilian Symposium on Medicinal Chemistry
Ouro Preto, MG
Lecture: "Metal compounds in Medicinal Chemistry"
Prof. Heloisa Beraldo

November 06 to November 09, 2010
BrazMedChem – Brazilian Symposium in Medicinal Chemistry
Federal University of Ouro Preto – MG
Mini-course: "Foundations in Medicinal Chemistry"
Prof. Eliezer J. Barreiro

November 03 and 04, 2010
IV Forum on Proteomics
National Cancer Institute – RJ
Round Table: Structural Proteomics as a tool in the development of drugs. Lecture: "Development of New Pharmaceuticals"
Prof. Eliezer J. Barreiro

October 19 to 22, 2010
Federal University of Roraima - RR
Mini-course: "Rational Process in Pharmaceutical Discovery"
Lecture: "Why don't our pharmaceuticals speak Portuguese?"
Prof. Eliezer J. Barreiro

October 05 to 08, 2010
I Pharmaceutical Integration Week of the Mid Araguaia Region
Federal University of Mato Grosso
Lecture: "Bioprospection and Medicinal Chemistry in the Search for New Pharmaceuticals"
Prof. Eliezer J. Barreiro

October 01, 2010
Malignant Hyperthermia 200 Symposium
Federal University of Rio de Janeiro

September 30, 2010
XI National Meeting of Pharmaceutical Chemistry Professors
Lecture: "The importance of Medicinal Pharmaceutical Chemistry in Interdisciplinarity"
Prof. Eliezer J. Barreiro

September 29, 2010
XII Biomedicine Week - UFRJ
Lecture: "Aspects of Innovation in Health: Pharmaceuticals"
Prof. Eliezer J. Barreiro

September 22, 2010
Cristalia Laboratories - Sao Paulo
Lecture: "JMF2-1 and JM25-1: pre-clinical evaluation for the development of a new anti-asthmatic pharmaceutical"
Prof. Marco Aurelio Martins

September 22, 2010
German Center of Innovation and Science
Natural Medications: the potential of Brazilian plants in traditional medicine
Lecture: "Use of natural products as building blocks, leads or preferred scaffolds in drug design"
Prof. Eliezer J. Barreiro

September 20, 2010
Anhembi Convention Palace
XVI Sao Paulo Congress of Pharmaceuticals
Symposium: "Planning and Development of Pharmaceuticals in Brazil"
Prof. Eliezer J. Barreiro

September 13 to 17, 2010
Federal University of Bahia
30th Pharmacy Academic Week - UFBA
Mini-course: "Principles of Medicinal Chemistry"
Lecture: "Interdisciplinarity of the Pharmaceutical Sciences"
Prof. Eliezer J. Barreiro

August 27, 2010.
INCA Update Seminars - Rio de Janeiro
Lecture: "Discovery and pre-clinical evaluation of new lidocaine analogs for the treatment of asthma."
Prof. Marco Aurelio Martins

August 24 and 25, 2010
Reboucas Convention Center – Faculty of Medicine Foundation – Sao Paulo
4th National Meeting on Innovation in Pharmaceuticals and Medications – ENIFarMed
Technical Session: "Excipients and Raw Materials"
Prof. Eliezer J. Barreiro
2nd Expo-FarMed
Prof. Eliezer J. Barreiro
Prof. Lidia Moreira Lima
Prof. Angelo da Cunha Pinto

August 23, 2010
UNESP Araraquara
57th Pharmaceutical Journey - UNESP
Mini-course: "The situation in the development of pharmaceuticals in Brazil"
Prof. Eliezer J. Barreiro

August 16 to August 20, 2010
Federal University of Alagoas
I Regional Pharmaceutical Journey - UFAL
Mini-course: "Planning of New Pharmaceuticals"
Prof. Eliezer J. Barreiro
Lecture: "State of the Art in Natural Products Chemistry in Brazil"
Prof. Angelo C. Pinto
Round table: "Therapeutic Innovations"
Prof. Lidia Moreira Lima

August 13, 2010
Department of Chemistry - Federal University of Sao Carlos
Lecture: "A few aspects of the planning of pharmaceuticals and metallopharmaceuticals"
Prof. Heloisa Beraldo

July 25 to 30, 2010
Federal University of Rio Grande do Norte
61st Annual Meeting of the Brazilian Society for the Progress of Science – SBPC
Mini-course: "Medicinal Chemistry"
Prof. Eliezer J. Barreiro

June 23 and 24, 2010
Brazilian Academy of Science
I INCTs Evaluation Seminar
Prof. Eliezer J. Barreiro

June 10, 2010
I Symposium on Research and Innovation – Oswaldo Cruz Institute – 110th Anniversary
Lecture: "Advancements and challenges in the development of new antiasthmatic medications: the lidocaine derivatives example"
Prof. Marco Aurelio Martins

May 28 to 31, 2010
Monte Real Resort Hotel – Aguas de Lindoia – SP
Mini-course: "Planning of new pharmaceutical candidates
33rd Annual Meeting of the Brazilian Chemistry Society
Prof. Eliezer J. Barreiro

May 27, 2010
I Meeting of the Research Laboratories Associated to the NanoBioAsthma Project - Federal University of Maceio and CAPES
Lecture: "Nanotechnology and the search for antiasthmatic candidates"
Prof. Marco Aurelio Martins

May 18, 2010
FIOCRUZ – FARMANGUINHOS
Institute of Technology in Pharmaceuticals
Meeting for the elaboration of scientific cooperation agreement
INCT-INOFAR/Farmanguinhos
Prof. Eliezer J. Barreiro/Prof. Angelo C. Pinto/ Prof. Lidia Moreira Lima

May 14 and 15, 2010
State University of Goias
II National Symposium in Technology and Development
Mini-course: "Rational planning of pharmaceuticals"
Lecture: "The role of Medicinal Chemistry in the development of new pharmaceuticals"
Prof. Eliezer J. Barreiro

May 13, 2010
Federal University of Rio de Janeiro
Integrated Seminars of the Institute of Biomedical Sciences (ICB)
Lecture: "The Pasteur Quadrant, innovation and the development of pharmaceuticals"
Prof. Eliezer J. Barreiro

May 10, 2010
Université Paris XIII
Lecture: "La coordination aux métaux: une stratégie pour la conception de nouveaux médicaments"
Prof. Heloisa Beraldo

May 04 and 05, 2010
Copacabana Mar Hotel – Rio de Janeiro
1st International Symposium on Challenges and New Technologies in Drug Discovery & Pharmaceutical Production
Lecture: "**INCT-INOFAR**: A Brazilian network for RD&I in pharmaceutical sciences"
Prof. Eliezer J. Barreiro

April 30, 2010
INPI - Rio de Janeiro-RJ
Lecture: "Radical innovation in Pharmaceuticals in the country: a personal perspective"
Prof. Eliezer J. Barreiro

March 24 and 25, 2010
Museum of Modern Art (MAM) – Rio de Janeiro
"FAPERJ 30 Years Expo"
Prof. Eliezer J. Barreiro

March 18, 2010
University of Itajai Valley
"10 years of the Master Program in Pharmaceutical Sciences"
Prof. Eliezer J. Barreiro

March 05, 2010
Federal University of Rio de Janeiro
"Horizons and Frontiers: challenges for Graduate Education and Research in UFRJ – 2010"
Prof. Eliezer J. Barreiro

PUBLISHING

101

INCT-INOFAR
Annual Activities Report
2010

INCT-INOFAR Publishing

National Journals

1. doi BARBOSA, M. C. M.; BARBOSA, A. P.; ROCCO, P. R. M. Uso de corticosteróide na síndrome do desconforto respiratório agudo em pacientes pediátricos. **Revista Brasileira de Terapia Intensiva**, v. 22, n. 4, p. 384-394, 2010.

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3. doi BATISTA, A. N. L.; BATISTA JR., J. M.; LÓPEZ, S. N.; FURLAN, M.; CAVALHEIRO, A. J.; SILVA, D. H. S.; BOLZANI, V. S.; NUNOMURA, S. M.; YOSHIDA, M. Aromatic compounds from three Brazilian Lauraceae species. Química Nova (Impresso), v. 33, n. 2, p. 321-323, 2010.

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11. doi GUERRANTE, R. S.; ANTUNES, A. M. S.; PEREIRA JR, N. Liderando através da inovação na biotecnologia - estudo de caso da Monsanto. **Economia & tecnologia** (UFPR), v. 21, n. 1, p. 87 – 99, 2010

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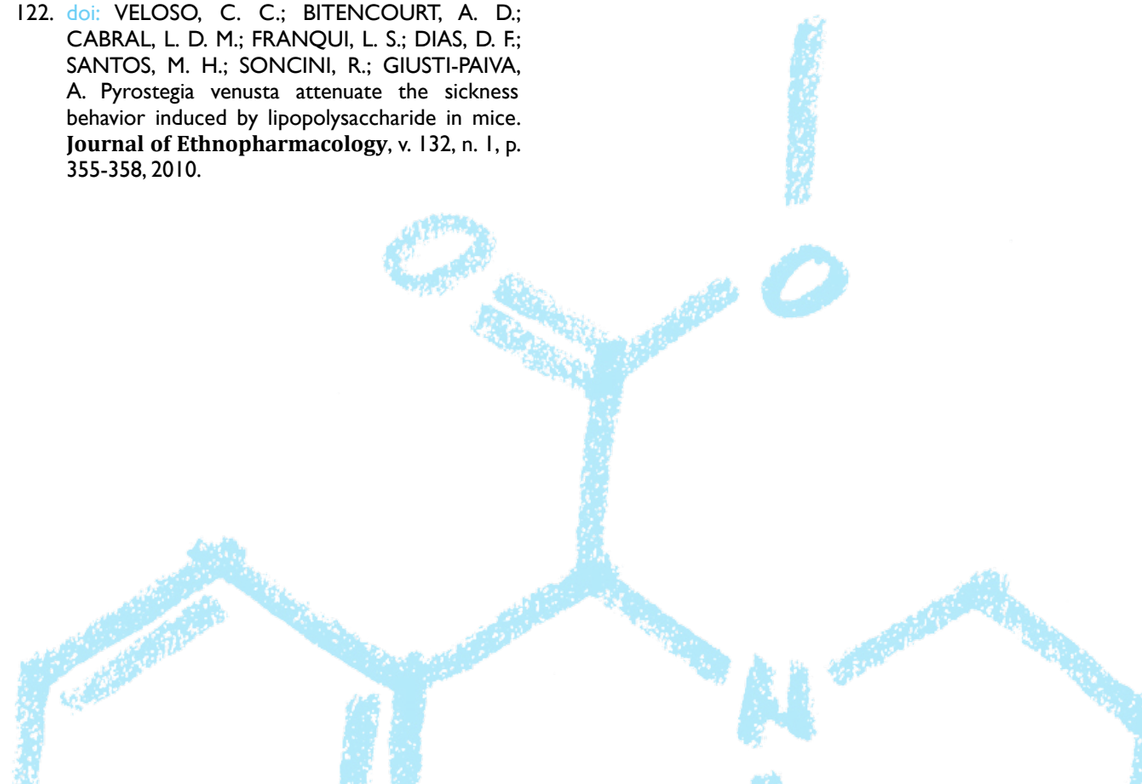

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CNPQ Technical Support Grant– AT NM
April to August 2010
Project: Development of new substances for the reduction of ventricular dysfunction, caused by arterial and pulmonary hypertension.
Advisor: Prof. Roberto Takashi Sudo
Institute of Biological Sciences (ICB)

ALEXANDRA BASILIO LOPES
CNPQ Technological Development Grant– DTI-3
June to September 2010
Project: Synthesis and evaluation of antinociceptive and anti-inflammatory activities of phenyl-pyridine-n-acylhydrazone compounds planned from imidazo [1,2-a] pyridine-n-acylhydrazone derivatives.
Advisor: Prof. Eliezer J. Barreiro
LASSBio

ARTHUR EUGEN KÜMMERLE
Junior Post-Doctoral CNPQ Grant-PDJ
September 2009 to March 2010
Project: Study of the Inclusion of LASSBio-579 in cyclodextrin.
Advisor: Prof. Eliezer J. Barreiro
LASSBio

CARLOS EDUARDO DA SILVA MONTEIRO
CNPQ Technological Development Grant– DTI-3
May 2010 to February 2011
Project: Multi-target activation: strategy for the symptomatic treatment of neuropathic pain.
Advisor: Prof. Roberto Takashi Sudo
Institute of Biological Sciences (ICB)

DANIEL NASCIMENTO DO AMARAL
CAPES Master Grant
March 2010 to February 2012
Project: Design, synthesis and pharmacological evaluation of new Sunitinib analogs.
Advisor: Prof. Dr. Lidia Moreira Lima
LASSBio

GIVANILDO SANTOS DA SILVA
CAPES Doctoral Grant
October 2009 to August 2010
Project: Studies for the discovery of new anti-influenza, neuramidase inhibitor prototypes.
Advisor: Prof. Dr. Lidia Moreira Lima
LASSBio

JESSICA SILVA DOS SANTOS
CNPQ Technical Support Grant– AT NM
From October to December 2010

LEANDRO LOUBACK DA SILVA
CAPES Doctoral Grant
October 2009 to August 2010
Project: Study of the effects of different *N*-acylhydrazone derivatives on the cell-to-cell interaction mechanisms and inflammatory mediators that are part of the atherosclerotic process.
Advisor: Prof. Dr. Ana Luisa Palhares de Miranda
LASSBio

LIDILHONE HAMERSKI CARBONEZI
CNPQ Junior Post-Doctoral Grant
August 2010 to January 2011
Project: Synthesis of Sunitinib.
Advisor: Prof. Dr. Angelo da Cunha Pinto
Institute of Chemistry (IQ)

LUCIA BEATRIZ TORRES
CNPQ Technological Development Grant– DTI-2
October 2010 to September 2011

NATALIA MEDEIROS DE LIMA
CNPQ Technical Support Grant– AT NS
August 2010 to April 2011

ROBERTA TESCH
CNPQ Technical Support Grant– AT NM
June to July 2010
Project: Studies of Molecular Modeling and Structural Planning of New Ligands for Adenosine Receptors.
Advisor: Prof. Dr. Carlos Alberto Manssour Fraga
LASSBio

THIAGO STEVANATTO SAMPAIO
CNPQ Technical Support Grant– AT NM
April 2009 to March 2010
Project: Design, synthesis and evaluation of cytotoxic properties of new TK inhibitor pharmaceutical candidate prototypes.
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

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ADRIANO SIQUEIRA VIEIRA
CNPQ Junior Post-Doctoral Grant
August 2009 to July 2011
Project: Synthesis of atorvastatin
Advisor: Prof. Dr. Luiz Carlos Dias
Institute of Chemistry

LEILA DE SOUZA CONEGERO
CNPQ Junior Post-Doctoral Grant
July 2010 to January 2011
Project: Synthesis of Fluoxetine
Advisor: Prof. Dr. Luiz Carlos Dias
Institute of Chemistry

UFC

BRUNO COELHO CAVALCANTI
CNPQ Junior Post-Doctoral Grant
From May to October 2010
Project: In vitro evaluation of cytotoxicological, genotoxic, and mutagenic potential of samples provided by INCT-INOFAR
Advisor: Prof. Dr. Manoel Odorico de Moraes
Faculty of Medicine

UFRGS

MOACIR KAISER
CNPQ Technological Development Grant– DTI-3
July 2009 to March 2010
Project: Study of functionalized n-fenilpiperazine derivatives as prototypes for the development of new atypical antipsychotics.
Advisor: Prof. Dr. Stela Maris Kuze Rates
Faculty of Pharmacy

UFMG

CAROLINA MALDONADO GALASSI
CNPQ Technological Development Grant– DTI-3
October 2009 to March 2010
Project: Benzaldehyde Semicarbazone (BS)
Advisor: Prof. Dr. Carlos Alberto Tagliatti
Faculty of Pharmacy

MARCUS VINICIUS DOS SANTOS
Technology Undergraduate Grant – ITI A
October 2009 to March 2010
Project: Benzaldehyde Semicarbazone (BS)
Advisor: Prof. Dr. Carlos Alberto Tagliatti
Faculty of Pharmacy

WALLACE CARVALHO FERREIRA
CNPQ Technical Support Grant– AT NM
August 2009 to January 2010
Project: Benzaldehyde Semicarbazone (BS)
Advisor: Prof. Dr. Marcio de Matos Coelho
Faculty of Pharmacy

USP / Ribeirao Preto

GIULIANA BERTOZI FRANCISCO
CNPQ Technical Support Grant– AT NM
September 2010 to August 2011
Project: Benzaldehyde Semicarbazone (BS)
Advisor: Prof. Dr. Fernando de Queiroz Cunha
Faculty of Medicine of Ribeirao Preto

UFG

ANA MARIA CALADO DOS SANTOS
CNPQ Technical Support Grant – AT NM
July 2010 to June 2011
Project: "*In silico*" prediction and "*in vitro*" production through bioconversion of human metabolites of pharmaceutical prototype candidates.
Advisor: Prof. Dr. Valeria de Oliveira
Faculty of Medicine

Finished doctoral theses

1. **Amanda Coelho Danuello.** Estudos computacionais e sintéticos visando o planejamento racional de novos agentes anticolinesterásicos. (*Computational and synthetic studies for the rational planning of new anticholinesterasic agents*). 2010. Thesis (Doctorate in Chemistry) – State University of Sao Paulo Julio de Mesquita Filho. *Advisor:* Vanderlan da Silva Bolzani; *Co-advisor:* Carlos Alberto Manssour Fraga.

2. **Andressa de Freitas.** Papel da enzima heme Oxigenase-1 na patogênese da sepse grave. (*Role of the heme Oxygenase-1 enzyme in the pathogenesis of acute sepsis*). 2010. Thesis (Doctorate in Pharmacology) – University of Sao Paulo / Ribeirao Preto, Foundation for Research Support of the State of Sao Paulo. *Advisor:* Fernando de Queiroz Cunha.

3. **Caroline da Costa Silva Gonçalves.** Síntese total das basiliskamidas A e B e do fragmento C1-C9 da dictiostatina. (*Total synthesis of basiliskamides A and B and of the C1-C9 fragment of dictyostatin*). 2010. Thesis (Doctorate in Chemistry) – State University of Campinas, Foundation for Research Support of the State of Sao Paulo. *Advisor:* Luiz Carlos Dias.

4. **Dimas Jose da Paz Lima.** Síntese do fragmento C11-C26 do potente agente antitumoral dictiostatina. (*Synthesis of the C11-C26 fragment of the powerful antitumoral agent dictyostatin*). 2010. Thesis (Doctorate in Chemistry) – State University of Campinas, Foundation for Research Support of the State of Sao Paulo. *Advisor:* Luiz Carlos Dias.

5. **Gerardo Magela Vieira Junior.** Contribuição ao estudo dos metabólitos secundários do gênero *casearia* e de algumas de suas atividades biológicas. (*Contribution to the study of secondary metabolites of the casearia genus*). 2010. Thesis (Doctorate in Chemistry) – State University of Sao Paulo / Araraquara. *Advisor:* Vanderlan da Silva Bolzani.

6. **Indianara Maria Araujo do Nascimento**. Terapia com células mononucleares derivadas da medula óssea em modelos experimentais de lesão pulmonar aguda de etiologia pulmonar e extrapulmonar. (*Therapy with mononuclear cells derived from bone marrow in experimental models of acute pulmonary lesion of pulmonary and extrapulmonary etiology*). 2010. Thesis (Doctorate in Biological Sciences – Physiology) - Federal University of Rio de Janeiro. *Advisor:* Patricia Rieken Macedo Rocco

7. **Jorge de Albuquerque Calasans Maia.** Novo agonista alfa-2 adrenérgico derivado imidazolidínico e sua atividade antinociceptiva. (*New alpha-2 adrenergic agonist imidazolidine derivative and its antiociceptive activity*). 2010. Thesis (Doctorate in Medicine – General Surgery) - Federal University of Rio de Janeiro. *Advisor:* Roberto Takashi Sudo; *Co-advisor:* Gisele Zapata-Sudo

8. **Jorge Lima de Magalhaes.** Estratégia governamental para internalização de fármacos & medicamentos em doenças negligenciadas. (*Governmental strategy for internalization of pharmaceuticals and medications in neglected illnesses*). 2010. Thesis (Doctorate in Chemical and Biochemical Processes Technology) – Federal University of Rio de Janeiro. *Advisor:* Adelaide Maria de Souza Antunes.

9. **Luana Braga Pontes**. Avaliação farmacológica de derivados metilenodioxifenilsulfonamídicos funcionalizados: novos inibidores de fosfodiesterases. (*Pharmacological evaluation of functionalized methylenedioxiphenylsulfonamide derivatives: new phosphodiesterase inhibitors*). 2010. Thesis (Doctorate in Biological Sciences – Pharmacology and Medicinal Chemistry) - Federal University of Rio de Janeiro, Coordination for Improvement of Higher Level Personnel. *Advisor:* Gisele Zapata-Sudo; *Co-Advisor:* Roberto Takashi Sudo.

10. **Marcos Pivatto.** Espectrometria de massas aplicada aos estudos de biossíntese de alcalóides de *senna spectabilis*. (*Mass spectrometry applied to alkaloid biosynthesis studies of senna spectabilis*). 2010. Thesis (Doctorate in Chemistry) – State University of Sao Paulo / Araraquara. *Advisor:* Vanderlan da Silva Bolzani.

11. **Pedro Leme Silva**. Estratégias ventilatórias em diferentes níveis de volemia em modelo de lesão pulmonar aguda. (*Ventilation strategies in different volemia levels in acute pulmonary lesion model*). 2010. Thesis (Doctorate in Biological Sciences -Physiology) - Federal University of Rio de Janeiro, Coordination for Improvement of Higher Level Personnel. *Advisor:* Patricia Rieken Macedo Rocco.

12. **Savio Moita Pinheiro**. Indução assimétrica remota na adição de enolatos de boro de metil cetonas quirais a aldeídos quirais e aquirais. (*Remote asymmetric induction in the addition of borum enolates of chiral methyl ketones to chiral and achiral aldehydes*). 2010. Thesis (Doctorate in Chemistry) – State University of Campinas, Foundation for Research Support of the State of Sao Paulo. *Advisor:* Luiz Carlos Dias.

13. **Thaiana da Cunha Ferreira Mendes.** Desenvolvimento de novas substâncias neuroativas derivadas do zolpidem para o tratamento da dor neuropática. (*Development of new neuroactive substances derived from Zolpidem for the treatment of neuropathic pain*). 2010. Thesis (Doctorate in Biological Sciences – Pharmacology and Medicinal Chemistry) - Federal University of Rio de Janeiro, National Council for Scientific and Technological Development. *Advisor:* Gisele Zapata-Sudo; *Co-Advisor:* Roberto Takashi Sudo.

Finished master dissertations

1. **Alexandra Basílio Lopes.** Síntese e avaliação das atividades antinociceptiva e anti-Inflamatória de compostos fenil-pirimidina-N-acilidrazonas planejados a partir de derivados imidazo [1,2-a] piridina-N-acilidrazonas. (*Synthesis and evaluation of antinociceptive and anti-inflammatory activity of the phenyl-pyrimidine-N-acylhydrazone compounds planned from imidazo [1,2-a] pyridine-N-acylhydrazone derivatives*). 2010. Dissertation (Master in Chemistry) - Federal University of Rio de Janeiro. *Advisor:* Eliezer Jesus de Lacerda Barreiro; *Co-advisor*: Carlos Alberto Manssour Fraga

2. **Amuzza Aylla Pereira dos Santos**. Conseqüências do parto cesáreo eletivo: um estudo epidemiológico no estado de Alagoas. (*Consequences of elective c-section birth: an epidemiologic study in the state of Alagoas*). 2010. Dissertation (Master in Health Sciences) – Federal University of Alagoas, Coordination for Improvement of Higher Level Personnel. *Advisor:* Magna Suzana Alexandre Moreira.

3. **Anansa Bezerra de Aquino.** Atividade analgésica e antiinflamatória da espécie aspidosperma tomentosum da família apocynaceae. (*Analgesic and anti-inflammatory activity of the aspidosperma tomentosus species of the apocynaceae family*). 2010. Dissertation (Master in Health Sciences) – Federal University of Alagoas, Foundation for Research Support of the state of Alagoas. *Advisor:* Joao Xavier de Araujo Junior. *Co-Advisor:* Magna Suzana Alexandre Moreira.

4. **Andressa Gusmao da Silva.** Metodologia para avaliação do potencial exportador de produtos petroquímicos importados. (*Methodology for evaluating the export potential of imported petrochemical products*). 2010. Dissertation (Master in Chemical and Biochemical Processes Technology) – School of Chemistry - UFRJ, Advisor: Adelaide Maria de Souza Antunes.

5. **Carla Cristina de Araujo**. O Exercício regular e moderado modula a resposta inflamatória aumentando a sobrevida em modelo experimental de sepse. (*Regular and moderate exercise modulates inflammatory response, increasing survival in an experimental sepsis model*). 2010. Dissertation (Master in Biological Sciences - Physiology) – Federal University of Rio de Janeiro, Coordination for Improvement of Higher Level Personnel. *Advisor:* Patricia Rieken Macedo Rocco.

6. **Carolina Martins Avila**. Estudos de modelagem molecular para o planejamento estrutural de novos protótipos antiinflamatórios inibidores da IKK-beta. (*Molecular modeling studies for the structural planning of new anti-inflammatory IKK-beta inhibitor prototypes*). 2010. Dissertation (Master in Biological Sciences – Pharmacology and Medicinal Chemistry) - Federal University of Rio de Janeiro. *Advisor:* Carlos Alberto Manssour Fraga; *Co-advisor:* Nelilma Correa Romeiro.

7. **Carolina Pereira Joia.** Análise farmacológica de novos derivados n-acilidrazônicos ciclizados. (*Pharmacological analysis of new cycled n-acylhydrazone derivatives*). 2010. Dissertation (Master in Biological Sciences – Pharmacology and Medicinal Chemistry) - Federal University of Rio de Janeiro. *Advisor:* Gisele Zapata-Sudo; *Co-Advisor:* Roberto Takashi Sudo.

8. **Claudia Quintino da Rocha.** Estudo químico e farmacológico de espécies flora Sulmineira. (*Chemical and pharmacological study of species of the Southern Minas Gerais flora*). 2010. Dissertation (Master in Chemistry) - Federal University of Alfenas. *Advisor:* Marcelo Henrique dos Santos.

9. **Cleverton Kleiton Freitas de Lima**. Estudo da modulação da resposta inflamatória e hiperalgésica induzida por carragenina e capsaicina por novos derivados imidazo-piridínicos. (*Study of the modulation of the inflammatory and hyperalgesic response induced by carrageenan and capsaicin through new imidazo-pyridine derivatives*). 2010. Dissertation (Master in Pharmacology and Medicinal Chemistry). Federal University of Rio de Janeiro, Coordination for Improvement of Higher Level Personnel. *Advisor:* Ana Luísa P. Miranda.

10. **Cristiane Machado**. A Influência da asma na movimentação ortodôntica – estudo experimental em ratos wistar. (The influence of asthma in orthodontic movement – experimental study in Wistar rats). 2010. Dissertation (Master in Odontology) - Federal University of Rio de Janeiro. *Advisor:* Patrícia Machado Rodrigues e Silva Martins

11. **Daniara Cristina Fernandes**. Estudo químico e atividade e biológica de *garcinia xanthochymus* (Clusiaceae). (*Chemical study and biological activity of garcinia xanthochymus (Clusiaceae*)). 2010. Dissertation (Master in Chemistry) State University of Sao Paulo / Araraquara. *Advisor:* Vanderlan da Silva Bolzani.

12. **Diana Dalzy Viveiros.** Inflamação alérgica modifica o fenótipo e a funcionalidade de fibroblastos pulmonares em cultura 3D. (*Allergic inflammation modifies the fenotype and functionality of pulmonary fibroblasts in 3D culture*). 2010. Dissertation (Master in Cellular and Molecular Biology) – Oswaldo Cruz Foundation. *Advisor:* Patricia Machado Rodrigues e Silva Martins.

13. **Diogo Guimaraes Marinho**. Avaliação do efeito anti-Inflamatório do leite da mangabeira. 2010. (*Evaluation of the anti-inflammatory effect of mangaba tree sap*). Dissertation (Master in Biological Sciences – Pharmacology and Medicinal Chemistry) – Federal University of Rio de Janeiro. *Advisor:* Patricia Dias Fernandes; *Co-advisor:* Maria Eline Matheus

14. **Diogo Jose Costa da Silva.** Avaliação da atividade antinociceptiva e anti-inflamatória de duas séries de derivados semi-sintéticos da (-)-cassina. (*Evaluation of the antinociceptive and anti-inflammatory activity of two series of semi-synthetic derivatives of (-)-cassin*). 2010. Dissertation (Master in Health Sciences) – Federal University of Alagoas, Coordination for Improvement of Higher Level Personnel. *Advisor:* Magna Suzana Alexandre Moreira.

15. **Felipe Saddy**. Modos de ventilação assistida reduzem a expressão de mediadores inflamatórios e fibrogênicos no pulmão em modelo de lesão pulmonar aguda. 2010. (*Assisted ventilation modes reduce expression of inflammatory and fibrogenic mediators in acute pulmonary disease model*). Dissertation (Master in Clinical Research) - Federal University of Rio de Janeiro. *Advisor:* Patricia Rieken Macedo Rocco.

16. **Fernando Passareli.** Preparação e caracterização de casearinas de *casearia sylvestris* como padrão fitoquímico. (*Preparation and characterization of casearins from casearia sylvestris as a phytochemical standard*). 2010. Dissertation (Master in Chemistry) – State University of Sao Paulo/Araraquara. *Advisor:* Vanderlan da Silva Bolzani.

17. **Giselle Azevedo Pereira da Silva**. Investigação da atividade depressora do sistema nervoso central de derivados n-acilidrazônicos LASSBio-785 e LASSBio-786. (*Investigation of the central nervous system depressant activity of n-acylhydrazone derivatives LASSBio-785 and LASSBio-786*). 2010. Dissertation (Master in Biological Sciences – Pharmacology and Medicinal Chemistry) - Federal University of Rio de Janeiro, Coordination for Improvement of Higher Level Personnel. *Advisor:* Roberto Takashi Sudo; *Co-advisor:* Gisele Zapata-Sudo.

18. **Jacqueline Soares da Silva**. Desenvolvimento de novas estratégias terapêuticas para melhora da fadiga muscular pós-Infarto do miocárdio. (*Development of new therapeutic strategies for the improvement of muscular fatigue post-myocardial infarction*). 2010. Dissertation (Master in Biological Sciences – Pharmacology and Medicinal Chemistry) - Federal University of Rio de Janeiro, National Council for Scientific and Technological Development. *Advisor:* Gisele Zapata-Sudo; *Co-advisor:* Roberto Takashi Sudo

19. **Marilia Valli**. Síntese e atividade biológica de compostos piridínicos, pirazidínicos e piridotiazínônicos. (*Synthesis and biological activity of pyridine, pyrazidine, and pyridothiazone compounds*). 2010. Dissertation (Master in Chemistry) – State University of Sao Paulo / Araraquara. *Advisor:* Vanderlan da Silva Bolzani.

20. **Miguel Divino da Rocha**. Síntese e avaliação farmacológica de novos híbridos moleculares 3-O-piperidinil-n-benzil-acilidrazônicos planejados como candidatos a fármacos simbióticos: anticolinesterásicos e anti-inflamatorios. (*Synthesis and pharmacological evaluation of new 3-O-piperidinil-n-benzyl-acylhydrazone molecular hybrids planned as symbiotic pharmaceutical candidates: anticholinesterasic and anti-inflammatories*). 2010. Dissertation (Master in Chemistry) - Federal University of Alfenas. *Advisor:* Claudio Viegas Junior.

21. **Milla Machado Fumian**. Estudo da atividade antiagregante plaquetária de derivados n-metilacilidrazônicos análogos ao LASSBio 785. (*Study of the anti-aggregating platelet activity of n-methylacylhydrazone derivatives analogous to LASSBio 785*). 2010. Dissertation (Master in Pharmacology and Medicinal Chemistry – Pharmacology) – Federal University of Rio de Janeiro, Coordination for Improvement of Higher Level Personnel. *Advisor:* Ana Luisa P. Miranda.

22. **Monica de Carvalho Muniz Chao.** O grau de lesão endotelial promove fibroelastogênese em modelo experimental de lesão pulmonar aguda. *(The degree of endothelial lesion promotes fibroelastogenesis in experimental acute pulmonary lesion model*). 2010. Dissertation (Master in Clinical Research - Federal University of Rio de Janeiro. *Advisor:* Patricia Rieken Macedo Rocco.

23. **Patricia Cardoso**. Detecção *in silico*, isolamento e caracterização estrutural dos constituintes micromoleculares antimaláricos e antioxidantes de *phomopsis cassiae*, fungo endofítico isolado de *senna spectabiliis*. (*In silico detection, isolation, and structural characterization of the antimalaric and antioxidant micromolecular constituents of phomopsis cassiae, endophytic fungus isolated from senna spectabiliis*). 2010. Dissertation (Master in Chemistry) – State University of Sao Paulo / Araraquara. *Advisor:* Vanderlan da Silva Bolzani.

24. **Paula Gizelle Czaikoski**. Falência de migração de neutrófilos na sepse grave induzida por pneumonia: papel da enzima heme oxigenase. (*Failure to migrate in neutrophils in acute sepsis induced by pneumonia: role of the heme oxygenase enzyme*). 2010. Dissertation (Master in Pharmacology) – University of Sao Paulo / Ribeirao Preto, Coordination for Improvement of Higher Level Personnel. *Advisor:* Fernando de Queiroz Cunha.

25. **Renata da Silva Zardo**. Efeito antitumoral de derivados sintéticos da convolutamidina A. (*Antitumoral effect of synthetic derivatives of convolutamydine A*). 2010. Dissertation (Master in Biological Sciences – Pharmacology and Medicinal Chemistry) – Federal University of Rio de Janeiro, Coordination for Improvement of Higher Level Personnel. *Advisor:* Patricia Dias Fernandes; Co-advisor: Maria Eline Matheus.

26. **Silvia Cellone Trevelin**. Papel do receptor toll-like 9 na falência de migração dos neutrófilos na sepse. (*Role of the toll-like 9 receptor in the failure to migrate of neutrophils in sepsis*). 2010. Dissertation (Master in Pharmacology) – University of Sao Paulo / Ribeirao Preto, Coordination for Improvement of Higher Level Personnel. *Advisor:* Fernando de Queiroz Cunha.

27. **Thays de Lima Matos Freire Dias**. Avaliação da atividade antiinflamatória e analgésica da espécie ximenia americana. (*Evaluation of the anti-inflammatory and analgesic activity of the ximenia americana species*). 2010. Dissertation (Master in Health Sciences) – Federal University of Alagoas, National Council for Scientific and Technological Development. *Advisor:* Magna Suzana Alexandre Moreira.

28. **Vanessa Mara Chapla**. Quimica e bioatividade do fungo endofitico *Phomopsis* Sp. isolado de *Cassia Spectabilis*. (*Chemistry and bioactivity of the endophytic fungus Phomopsis Sp. Isolated from Cassia Spectabilis*). 2010. Dissertation (Master in Chemistry) - Universidade Estadual Paulista/Araraquara. *Advisor:* Vanderlan da Silva Bolzani.

Project team

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Raquel Carvalho Montenegro – CV-Lattes
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Helio Jose Correa Barbosa – CV-Lattes
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